Program Highlights 1992

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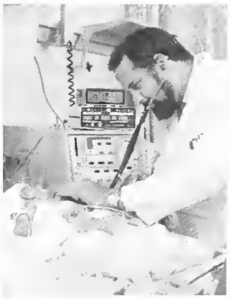
Resources

The mollusk Hermissenda crassicornis *is a critical organism for investigating neural aspects of behavior and learning. The NCRR-funded Laboratory Culture of* Hermissenda *at the Marine Biological Laboratory in Woods Hole, Massachusetts, maintains and distributes various strains of the laboratory-reared mollusks in life stages ranging from developing embryos to free-swimming larvae to mature adults. The work was supported by the Biological Models and Materials Research Program.*

Dr. Allan M. Kuzirian, Marine Biological Laboratory

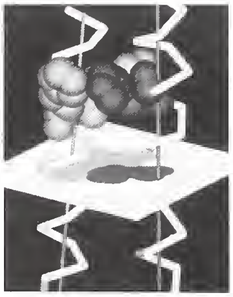


Dr. Lorry R. Frankel, director of pediatric critical care services at Lucile Salter Packard Children's Hospital at Stanford University in California, has helped develop a safe method for delivering the antiviral drug ribavirin to infants on mechanical ventilation. The work was supported by the General Clinical Research Centers Program.

Doug Peck, Lucile Salter Packard Children's Hospital at Stanford

Dr. Georgia Dunston (left), director of the NCRR-funded human immunogenetics laboratory at Howard University, Washington, DC, and postdoctoral trainee S. Predra Chundura are working to uncover the relationships between disease susceptibility and immunological factors in the African American population. This resource is supported by the Research Centers in Minority Institutions Program.

Jeffrey John Fearing, Biomedical Communications, Howard University College of Medicine



Graduate student Larry Bergman, of the GRIP Interactive Graphics System for Molecular Studies at the University of North Carolina in Chapel Hill, developed the software and created the image of interacting sidechains to the spiral-shaped helices in the protein myohemerthrin. The close, interlocking contact is illustrated in the projection onto the plane. The graphics resource is supported by the Biomedical Research Technology Program.

Larry Bergman, University of North Carolina at Chapel Hill

National Center for Research Resources

Program Highlights 1992

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Annual Report

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES
Public Health Service
National Institutes
of Health

Preface

The National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), develops and supports critical research technologies that underpin health-related research to maintain and improve the health of our nation's citizens. These technologies and resources include:

- Sophisticated instrumentation and technology;
- Specialized mammalian and nonmammalian models for studies of human diseases;
- Flexible support mechanisms to invest in new, emerging research opportunities;
- A cost-saving nationwide network of clinical research centers;
- Strong research infrastructure for predominantly minority institutions; and
- State-of-the-art equipment on a shared basis.

The multidisciplinary nature of NCRR-funded resources provides for a quick response to critical research needs. The Center's programs provide flexible approaches to solve new problems. Indeed, these approaches often precede and then complement research supported by NIH's categorical institutes and centers.

Through its support of multidisciplinary research NCRR is uniquely positioned to provide either primary research support or support in partnership with other NIH components to address emerging clinical and basic research needs.

Program Highlights 1992 describes the mission and significant accomplishments of each NCRR program and branch in fiscal year 1992. These achievements point to expanded efforts in clinical research; development of new animal and nonanimal models, new technologies, and instrumentation; improved research environments for minority investigators; and programs to encourage minority students to enter scientific careers.

Although it is uncertain what the next challenge confronting health research will be, NCRR stands ready to provide critical technologies needed to improve the nation's biomedical research capability and human health.

Judith L. Vaitukaitis, M.D.
Director, National Center for Research Resources
National Institutes of Health

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Selected Highlights 1992
National Center for Research Resources

Among the many Research Highlights described in the following pages, the topics listed below may be of special interest. These selected highlights represent some of the most significant advances achieved by NCRR-funded scientists in 1992. The broad range of topics illustrates the breadth of biomedical research that is supported by NCRR.

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Overview of Extramural Research Resources Activities

Program	Funding	Major Resources
General Clinical Research Centers Program	$ 127,111,000	• 75 General Clinical Research Centers • 45 Clinical Associate Physician Awards • 7 Minority Clinical Associate Physician Awards • 9 small business innovative research grants • Computerized database management and analysis systems (CDMAS) • cofunded MBRS grant to Meharry Medical College GCRC • cofunded Science Education Partnership Award
Biomedical Research Technology Program	$ 46,264,000	• 62 Biomedical Research Technology Resource Centers • 9 research project grants • 5 resource-related project grants • 29 small business innovative research grants • 11 small grants • PROPHET computer network • 2 predoctoral trainee awards
Comparative Medicine Program	$ 72,410,000	• 7 Regional Primate Research Centers • 35 Laboratory Animal Research Resource Centers • 30 research project grants • 4 resource-related research project grants • 48 animal facility improvement awards • 12 research career awards in laboratory animal sciences • 21 postdoctoral research training programs • 3 small business innovative research grants • Chimpanzee Breeding and Research Program • Specific-Pathogen-Free Rhesus Monkey Breeding and Research Program
Biomedical Research Support Program	$ 22,810,000	• Biomedical Research Support Grants awarded to 104 institutions • 39 Shared Instrumentation Grants • 385 Minority High School Student Research Apprentice Program awards to support 3,066 students and 578 teachers • 12 Science Education Partnership Awards administered for the NIH Office of the Director • 5 Science Teaching Enhancement Awards administered for the NIH Office of the Director
Biological Models and Materials Research Program	$ 8,368,000	• 5 Biological Models Research Centers • 23 research project grants • 2 resource-related research projects • 2 resource centers • 1 small business innovative research grant • 14 small research grants
Research Centers in Minority Institutions Program	$ 23,472,000	• 18 RCMI awards • cofunded three grants to establish Minority Centers for Dental Research • cofunded Center for African American DNA Genomic Database • sponsored International Symposia on AIDS in Minority Populations and Diabetes in Minority Populations • 3 grant awards to develop Environmental Health Science/Toxicology Centers • cofunded Minority High School Student Research Apprentice Program • cofunded Biomedical Research Careers Symposium for Minority Students
Total Extramural	$ 300,435,000*	

*In addition, $3,169,000 of reimbursable authority from other Federal agencies was obligated by NCRR for FY 1992.

General Clinical Research Centers Program

Program Description

The General Clinical Research Centers (GCRC) Program of the National Center for Research Resources significantly expands opportunities for biomedical achievements by clinical investigators who receive their primary research funding from other components of the National Institutes of Health (NIH). In FY 1992 GCRC Program funding supported the network of GCRC's and other related activities with more than $127 million.

Investigators who use the resources across the network of GCRC's continue to be at the forefront of biomedical research, as evidenced by the level of primary research support they receive from NIH and other peer-reviewed sources and their numerous, impressive publications of research results in the scientific literature. The 75 funded centers in the program's national network extend the range and intensity of clinical research by complementing the funding provided to investigators who study cancer, AIDS, heart diseases, diabetes, aging, alcoholism, drug addiction, arthritis, infectious diseases, and mental disorders; develop new diagnostic tests and therapies; and investigate scores of other health problems affecting both children and adults and involving the lungs, blood, kidneys, gastrointestinal tract, muscles, and eyes, mirroring the research missions of all the other NIH institutes. In FY 1992, 7,063 investigators carried out 4,729 clinical research projects in the GCRC's. The centers offer a research infrastructure, often otherwise unavailable, that includes specialized research nurses, research dietitians, biostatisticians, computer hardware and software systems for data management and analyses, sophisticated laboratories, and customized facilities and professional staffing for inpatient and outpatient research.

Conceptually the GCRC Program is analogous to a research-intensive hospital with more than 500 beds distributed geographically, reflecting the population density of the continental United States. It constitutes the extramural NIH counterpart of the Warren Grant Magnuson Clinical Center on the NIH campus in Bethesda, Maryland. In FY 1992 the program was involved in approximately 30,000 hospital admissions, 100,000 research inpatient days, and 200,000 outpatient research visits.

To help continue the availability of physicians who are well-trained, independent clinical investigators, the program is significantly involved in clinical research training and career development. Since 1974 the GCRC Program has sponsored the Clinical Associate Physician (CAP) Program, a competitive supplement to GCRC grants that provides up to 3 years of support to a physician for training under a senior clinical scientist mentor. To date,

An immunological examination of tumor tissue of squamous cell carcinoma of the head and neck enables investigators to predict if the tumor is likely to reappear after initial removal. Drs. Gregory T. Wolf (left) and Thomas E. Carey at the University of Michigan in Ann Arbor have found tumor recurrence in 78 percent of patients whose original tumor had lost the ABH blood group antigens and in 58 percent of patients whose tumors showed increased amounts of the A9 antigen.

Thomas Treuter, University of Michigan, Ann Arbor

267 physician-scientists have completed the CAP Program, and these graduates fill important positions in academic medical research. In 1991 the GCRC Program initiated the Minority Clinical Associate Physician (MCAP) Program to attract underrepresented minority physicians to clinical research at GCRC sites; seven MCAP awards were made in FY 1992.

To honor distinguished GCRC investigators, the GCRC Program presents an annual Award for Excellence in Clinical Research. In 1992 Dr. Fred Rosen, professor of pediatrics at Harvard University and formerly program director of the GCRC at Children's Hospital in Boston, Massachusetts, received the fourth annual prize. Dr. Rosen's major contributions during his 35-year scientific career have been in the area of immunodeficiency syndromes, most notably genetic defects of the complement system and primary immunodeficiency diseases such as Wiskott-Aldrich syndrome, X-linked agammaglobulinemia, and hyper IgM syndrome.

In 1991 the U.S. Department of Health and Human Services issued a statement of objectives titled *Healthy People 2000*. As the following "Research Highlights" illustrate, research progress made at GCRC's during 1992 should help to advance our national health objectives toward meeting the goals of *Healthy People 2000*.

Research Highlights

AIDS

Nonreactive Antibodies May Cause Misdiagnosis of HIV Infection. Tests for HIV infection depend on detection of specific antibody in serum. HIV infection is missed in some individuals who appear seronegative on the standard clinical enzyme-linked immunoadsorbent and Western blot assays. This apparent immunologically silent period following infection may last for months and, in rare cases, has been reported to be as long as 3 years. By an indirect immunofluorescence assay using live HIV-infected T-cells, researchers at the University of Texas General Clinical Research Center in Galveston found that each of four infected individuals who were seronegative by the standard tests did possess antibody against native HIV proteins expressed on infected cells. The antibodies reacting with native HIV antigenic epitopes were of the IgG isotype. These results show that infected individuals who appear seronegative by standard assays may actually be seropositive and that different types of assays using native antigenic epitopes may be required for screening.

Testing Potential AIDS Vaccine. Researchers at the New York University GCRC in New York City investigated immune response to a vaccine containing the HIV viral protein gp160. Subjects received immunizations with four increasing doses of gp160 or a hepatitis B viral antigen as a control antigen. All subjects were seropositive for both HIV and hepatitis B and had more than 400 CD4 cells per microliter of blood, which is important for a proper immune response. The subjects were immunized at 0, 1, 3, 6, 9, and 12 months and were followed monthly for immune responses to HIV. The investigators found that the recipients of the gp160 vaccine developed new or enhanced immune responses to HIV antigens, but the recipients of the hepatitis vaccine did not. Lymphocytes from vaccine recipients also developed the ability to produce the important lymphokine IL-2 when stimulated with gp160 in vitro. The investigators point out that vaccinating subjects who are already chronically infected with HIV could induce immune responses to HIV antigens that the infection itself had not stimulated. Further studies are required to evaluate whether the vaccine can retard or prevent progression to AIDS in HIV-infected individuals or prevent HIV infection in noninfected individuals.

Evaluation of New Drugs Against AIDS. In cooperation with the NIH-funded AIDS Clinical Trials Group, investigators at GCRC's continue to devote major efforts and resources to test drugs that may be effective against HIV or complications of AIDS.

Drugs currently under study include interferon; interleukin-2; acyclovir; pentamidine; spiramycin; rifampin; ciprofloxacin; clofazimine; ethambutol; amikacin; granulocyte-macrophage colony-stimulating factor; recombinant soluble CD4 (receptin); 2′,3′-dideoxyinosine (ddI); dideoxycytidine (ddC); 3′-azido-2′,3′-dideoxyuridine (AzdU); 3′-deoxy-3′-fluorothymidine; gancyclovir; gamma-globulin; trimethoprim; sulfamethoxazol; trimetrexate; foscarnet; clindamycin; primaquine; zidovudine (azidothymidine or AZT); and itraconazole.

Many studies have progressed from phase I clinical evaluations to phases II and III and are being performed at clinical centers throughout the United States.

Serum Zinc and Copper Levels May Predict AIDS Progression. In a study at the Johns Hopkins University Outpatient GCRC in Baltimore, Maryland, baseline dietary, serum, and tissue levels of copper and zinc were determined in groups of homosexual men to investigate the relationship of these factors to HIV-1 seropositivity and subsequent progression to AIDS. During a mean followup period of 2.5 years, 54 asymptomatic HIV-1 seropositive men who later progressed to AIDS were compared with 54 HIV-1 seropositive subjects who did not progress and 54 seronegative men. Serum levels of copper and zinc were estimated from frozen serum samples, tissue levels from stored toenail samples, and dietary intakes from a semiquantitative food frequency questionnaire. Neither dietary copper and zinc nor their levels in toenails were associated with HIV-1 seropositivity or progression to AIDS. However, serum copper levels were significantly higher in HIV-1 seropositive individuals who progressed to AIDS than in the men who were seropositive but did not progress and those who were seronegative. Conversely, serum zinc levels were lower in the seropositive progressors than in the seropositive nonprogressors and the seronegatives. The GCRC investigators suggest that serum copper and zinc levels may be useful markers of progression to AIDS in HIV-1 seropositive individuals.

Arthritis

Nonsurgical Removal of Inflamed Tissue in Diseased Joints. Investigators at the GCRC at Baylor College of Medicine in Houston, Texas, are exploring innovative treatments for rheumatoid arthritis. In one such treatment the inflamed tissue around a diseased joint is removed nonsurgically by a process called radiation synovectomy. This procedure, which involves the use of a substance known as dysprosium-165 ferric hydroxide macroaggregate, was performed on 20 knees in 17 rheumatoid arthritis patients. An average of 300 millicuries of the radioactive substance was injected into each affected joint. One year after treatment all 20 knees were examined and 80 percent showed good-to-excellent response to therapy.

At 2 years, only 18 knees were available to followup and 56 percent of them showed a good-to-excellent response. The investigators concluded that dysprosium-165 ferric hydroxide macroaggregate is clinically effective for the treatment of early rheumatologic disorders.

Monoclonal Antibody Therapy for Rheumatoid Arthritis. Researchers at the GCRC at the University of Texas Southwestern Medical Center in Dallas are studying the safety and efficacy of a monoclonal antibody called BIRR1 in patients with chronic rheumatoid arthritis. BIRR1 is directed against a cell adhesion molecule known as ICAM-1. Adhesion molecules have a crucial role in the accumulation of leukocytes at inflammatory sites, such as the rheumatoid joint lining and joint spaces. Two patients have been treated with a low dose of BIRR1 and one with an intermediate dose. None showed any adverse effects. The patient receiving the intermediate dose had no more morning stiffness and fewer tender and swollen joints. Should similar results be found in additional patients, this type of treatment may be an important therapeutic advance for patients with rheumatoid arthritis and other systemic inflammatory disorders.

Bone

Calcium Supplementation Benefits Prepubertal Children. Weakened bones cause numerous injuries in the elderly, and many studies have addressed the urgent problem of how best to prevent the debilitating osteoporosis that especially affects women after menopause. Some studies have suggested that increased dietary calcium intake during childhood results in stronger adult bones. GCRC investigators at Indiana University School of Medicine in Indianapolis have studied a group of 70 pairs of identical twins, 6 to 14 years old. Of these, 45 pairs completed the study. One member of each pair of twins received calcium supplementation, corresponding to a total calcium intake of 1,612 mg/day. The other twin received 908 mg calcium/day. The researchers measured bone mass by photon absorptiometry of the radius (a bone in the forearm), spine, and hip. In children who did not reach puberty during the study, the calcium-supplemented twins had higher bone masses than the nonsupplemented ones. Children who went through puberty during the study or had gone through puberty before the study had insignificant benefits from calcium supplementation. For all the children the combined differences in bone mass always favored the calcium-supplemented twin. If the gain persists, peak bone mass will be enhanced and the risk of future fracture should be reduced.

Cancer

Experimental Therapy for Brain Tumors. Investigators at Stanford University GCRC in California followed up on anecdotal reports suggesting that patients who had been operated on for the malignant brain tumor glioblastoma multiforme and became intracranially infected with bacteria lived longer than noninfected patients. In phase I studies the researchers injected a mixture of the lymphokine IL-2 and killed *Corynebacterium parvum* together with a protein carrier matrix named "therapeutic implant" directly into the tumors of patients with recurrent glioblastoma. When injected into the brain the drugs diffuse slowly from the carrier matrix, providing increased concentration and extended exposure of the drugs at the disease site. Compared to the usual mean survival time of 8 to 12 weeks after tumor recurrence, patients who had received the experimental treatment survived two to three times longer. Approximately 40 to 50 percent of the patients remained clinically stable with no radiographic evidence of early disease progression.

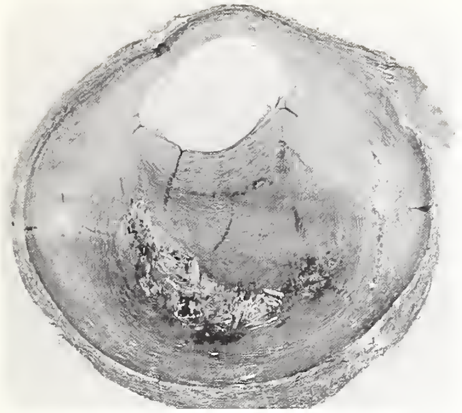
Collaborative Studies of Inherited Thyroid Cancer. For the past 15 years investigators at the Johns Hopkins University Outpatient GCRC in Baltimore, Maryland, have carried out studies of patients with inherited medullary thyroid cancer (MTC) to develop precise methods of diagnosis and optimal therapy, and to determine molecular events of tumor progression. In collaboration with researchers at Washington University in St. Louis, Missouri, the Baltimore investigators studied more than 100 patients with inherited MTC and more than 300 persons at risk for inheriting the MTC gene. These studies led to the development of a sensitive combination provocative test for abnormal secretion of the thyroid hormone calcitonin. The new test makes it possible to diagnose hereditary MTC at a very early stage. These studies also contributed to the definition of the third genetic MTC syndrome to be discovered, isolated familial MTC. These careful, long-term, GCRC-based outpatient studies have substantially improved the understanding of the natural history and pathogenesis of MTC, and have led to improved detection and treatment of persons with these inherited and sporadic disorders.

Cardiovascular Studies

Dietary Cholesterol Increases Plasma LDL. In a study at the GCRC at the University of California, San Francisco, investigators fed diets of defined fat and cholesterol content to men, 25 to 35 years old, who had normal plasma levels of fat and cholesterol. Subsequently they determined the effects on plasma lipoproteins and plasma lipid metabolic enzymes. Much of the cholesterol ester in plasma, including low-density lipoprotein (LDL)-cholesterol ester, is synthesized in plasma by the action of lecithin:cholesterol acyltransferase activity and then transferred from its site of synthesis in high-density lipoprotein to other lipoproteins by the action of the plasma cholesterol ester transfer protein (CETP). In this study dietary hypercholesterolemia was associated with a significant increase in the transfer of

Scientists at the Pediatric Clinical Research Center at Johns Hopkins Medical School in Baltimore, Maryland, break down and analyze foods to identify the components that cause allergies. Dr. Jan Bernhisel-Broadbent talks with two children who participated in these studies of food allergies.

Gordon Swan, Johns Hopkins University Hospital



Atherosclerotic deposits called plaque can close off coronary arteries, which supply blood to the heart muscle. This condition is the principal contributor to heart attacks, the number-one cause of death in Western countries. In this photo of a clogged artery the light crystalline particles consist of cholesterol. The darker spots are calcium. Dr. Greg Brown and his colleagues at the University of Washington School of Medicine and the GCRC in Seattle have shown that cholesterol-lowering drugs in men with atherosclerosis clear up clogged arteries so a more adequate blood supply can reach the heart.

Dr. Greg Brown, University of Washington

cholesterol esters to LDL mediated by CETP, thus indicating that dietary cholesterol is an important signal of increasing plasma LDL levels.

Enzyme Inhibitor Improves Survival of Patients With Heart Disease. Scientists at the University of Rochester GCRC in Rochester, New York, participated in a multicenter, double-blind clinical drug trial named "SOLVD." In this study the researchers evaluated the effect of an angiotensin-converting enzyme inhibitor (enalapril) on the survival of patients with left heart failure. The patients were randomized into one of two trials: the prevention trial included patients with no symptoms of, and no treatment for, congestive heart failure (CHF); and the treatment trial included patients who had been diagnosed as having CHF, had symptoms, and were being treated for CHF. In the treatment trial enalapril resulted in a 16-percent reduction in mortality, indicating a beneficial effect in patients with symptomatic CHF. In the prevention trial, the patients taking enalapril had 37 percent fewer incidences of CHF, a 36-percent reduction in hospitalizations for CHF, and a trend toward lower mortality.

Diabetes

Early Insulin Therapy May Prevent Diabetes in High-Risk Individuals. Investigators at the GCRC of Children's Hospital in Boston, Massachusetts, have found that early insulin therapy may preserve beta-cell function and prevent or delay the onset of clinical diabetes mellitus in high-risk individuals. The researchers studied first-degree relatives of patients with type 1, or insulin-dependent, diabetes who were at high risk of developing diabetes within 3 years. The subjects received daily low doses of insulin subcutaneously and 5-day courses of intensive, continuous intravenous insulin every 9 months. None of the treated patients developed diabetes or glucose intolerance, but most of the untreated control patients developed diabetes.

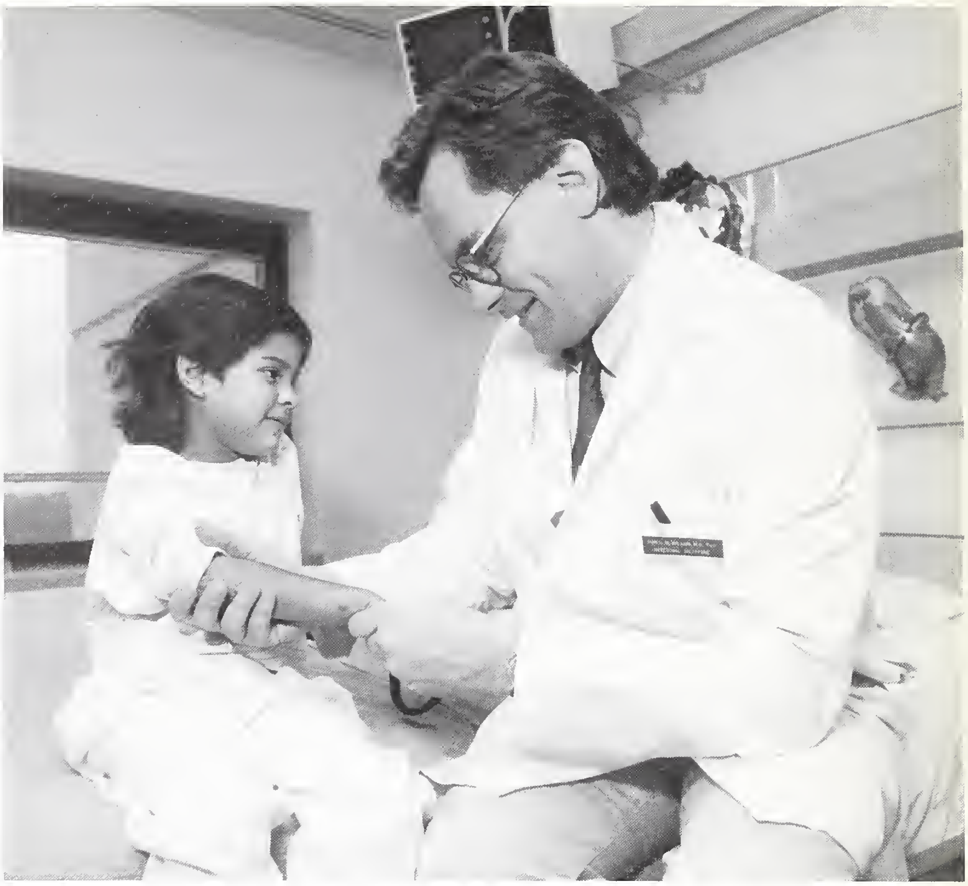
Development of Diabetes in Women With Previous Gestational Diabetes. GCRC investigators at Northwestern University in Chicago, Illinois, have followed for 8 to 10 years a group of more than 275 women who had gestational diabetes mellitus (GDM) during pregnancy. Glucose tolerance was evaluated 3 to 6 months after delivery and is now followed annually. This ongoing study is showing that women who had GDM are at a higher risk of developing diabetes earlier in their followup than was previously recognized. Within 1 year 15 to 20 percent of the women developed diabetes, and after 5 years approximately 50 percent had diabetes. Women with GDM tend to be older and more obese than the average pregnant woman but neither age nor degree of obesity have been strong predictors of the course of glucose tolerance during the first 5 years of followup. In the continuing followup studies the researchers will evaluate whether these women, like those with non-insulin-dependent diabetes, are at risk of developing cardiovascular diseases.

Endocrine Disorders

Hormone Treatment for Congenital Hyperinsulinism. Researchers at the GCRC at Children's Hospital of Philadelphia in Pennsylvania are investigating the use of octreotide, a long-acting analog of the hypothalamic hormone somatostatin, for treatment of congenital hyperinsulinism. Infants born with this disorder are unable to adequately reduce insulin secretion when their blood sugar concentration falls during fasting. As a result, they have persistent high insulin and low blood sugar concentrations, which may cause seizures and brain damage. When infants with congenital hyperinsulinism were given subcutaneous injections of octreotide, which inhibits insulin secretion, they had a marked increase in blood sugar levels. However, after two or three injections octreotide lost its effect. The investigators suggest that octreotide may be a useful adjunct to presurgical therapy. Surgery to remove 95 percent of the pancreas is one of the few therapeutic options for these children. Further studies may provide ways to overcome the loss of octreotide efficacy after a few doses and improve the ability to manage hyperinsulinism patients without surgery.

Genetic Diseases and Gene Therapy

Improved Treatment of Gaucher Disease. Gaucher disease is the most common glycolipid storage disease. It is caused by the absence of a degradative enzyme and characterized by enlargement of the liver and spleen by accumulating fatty substances called glycolipids, involvement of the bone marrow, and widespread skeletal changes. The severity of the disease varies greatly, ranging from a symptomatic state to a rapidly progressing disorder that is fatal within the first year of life. For the past 15 years investigators at the GCRC of Scripps Research Institute in La Jolla, California, have been attempting to treat this disease by administering the missing enzyme, glucocerebrosidase, to patients. Recently the



At the University of Michigan Medical Center in Ann Arbor scientists are attempting to treat an inherited form of elevated blood cholesterol known as familial hypercholesterolemia (FH) by genetic engineering techniques. The principal investigator Dr. James M. Wilson examines a young girl with FH.

Linda Goings, University of Michigan

researchers have begun treating 10 patients with a novel form of the enzyme that has been modified so it is preferentially taken up by macrophages. The patients' livers, measured by ultrasound or quantitative MRI scanning, have decreased in size dramatically. In one patient a 30-percent shrinkage of a massively enlarged liver was observed in only 3 months. These studies may bring about the first effective therapy of Gaucher disease.

Gene Therapy of Familial Hypercholesterolemia and Melanoma. Clinical trials involving gene therapy have begun at the University of Michigan Medical Center GCRC in Ann Arbor. Initiation of the trials was greatly facilitated by completion of the Human Applications Laboratory (HAL), which was formally dedicated in February 1992. The HAL is housed within the GCRC and serves as a core laboratory for investigators with gene therapy protocols. HAL is a state-of-the-art facility that operates in compliance with the Good Manufacturing Practices guidelines specified by the Food and Drug Administration (FDA). The laboratory is designed specifically to produce FDA-approved viruses—such as recombinant retroviruses and adenoviruses—for human gene therapy trials right next to the clinical setting.

Two groups of Michigan investigators are conducting gene therapy trials at the GCRC. One group is attempting to treat familial hypercholesterolemia, an inherited disease marked by dangerously high blood levels of cholesterol, by using a modified retrovirus to insert a corrected version of a defective gene into the patients' liver cells. The gene encodes a protein involved in removing LDL-cholesterol—the harmful form of cholesterol—from the blood for degradation in the liver. The other group of researchers injects DNA encased in fat globules called liposomes directly into melanoma skin tumors. The injected DNA contains a gene for making a cell surface protein, known as a histocompatibility antigen, that will make the tumor susceptible to destruction by the patient's immune system.

Diseases in Newborn Infants

Heparin Anticoagulation Studies in Newborns. Investigators at the Pediatric GCRC of the University of Colorado in Denver have studied causes and prevention of the thromboses, or blood clots, that often form in major blood vessels of high-risk preterm infants. The thromboses occur especially in connection with the use of central venous or arterial catheters for extended periods of time. Babies with indwelling umbilical artery catheters received a

Drs. Ernest Beutler and Andrea Kay are analyzing different genetic forms of the enzyme glucose-6-phosphate dehydrogenase (G6PD) at Scripps Research Institute in La Jolla, California. G6PD deficiency can lead to hemolytic anemia, or premature destruction of red blood cells. Newborn infants with G6PD deficiency may require emergency replacement of their blood. A better understanding of the structure of the gene and its mutations may lead to improved diagnosis and treatment of the disease.

Mark Dastrup, Scripps Research Institute

continuous infusion of the anticoagulant heparin at the usual therapeutic dose. Babies with an early severe deficiency of the coagulation regulatory protein known as protein C had a significant chance of developing catheter-related thromboses. Infusion of therapeutic doses of heparin resulted in high heparin levels in some babies and these did not develop symptomatic large vessel thromboses. In contrast, other babies, especially those with bacterial infections or those who had diabetic mothers, did not achieve high heparin levels, and thromboses were not prevented. The investigators conclude that effective heparin anticoagulation in newborns can only be accomplished in conjunction with monitoring plasma heparin levels.

Erythropoietin Therapy Relieves Anemia in Premature Infants. Premature infants, delivered at less than 32 weeks of gestation, often develop anemia that is caused by too low concentrations of the hormone erythropoietin, which stimulates red blood cell production by the bone marrow. The infants may show increased heart rate, poor weight gain, failure to feed, and sudden cessation of breathing. Investigators at the University of Utah GCRC in Salt Lake City compared the efficacy of erythrocyte transfusion and erythropoietin administration in alleviating this type of anemia in a prospective, randomized trial of 19 preterm infants. They found that both treatments were equally effective in increasing the number of red blood cells and hemoglobin concentration. This study is the first randomized trial that demonstrates the efficacy of recombinant erythropoietin in newborns with anemia of prematurity.

Organ Transplantation

Determining Priority for Liver Transplantation. Patients with chronic liver disease often die before a liver becomes available for transplantation. The United Network for Organ Sharing, which coordinates effective use of organs across the country, determined that approximately 25 percent of patients awaiting liver transplantation developed life-threatening complications during the waiting period and did not survive. Investigators at Virginia Commonwealth University's Medical College of Virginia in Richmond, trying to determine which potential liver recipients have the most urgent need, report that the metabolism of lidocaine may be used as an indicator of urgency.

Neuropathologist Dr. Bernardino Ghetti and his colleagues at the University of Indiana School of Medicine in Indianapolis study the molecular genetics of familial Alzheimer's disease. Here Dr. Ghetti is examining a microscope slide containing brain tissue from a patient who died in his forties of familial Alzheimer's disease.

Indiana University School of Medicine

Lidocaine, a commonly used local anesthetic and antiarrhythmic drug, is metabolized by the liver into monoethylglycine-xylidide, MEG-X, which is readily measured. The researchers administered lidocaine intravenously to 46 patients with cirrhosis of the liver who had been referred to the Medical College of Virginia for liver transplantation. MEG-X was determined in the blood 15 minutes later. The MEG-X values were significantly lower in patients who developed life-threatening complications than in patients without complications. Other liver metabolism indicators, such as albumin, prothrombin time, or bilirubin, showed no significant differences among patients.

New Antibody Prevents Graft Rejection. GCRC investigators at the University of Kentucky College of Medicine in Lexington are testing the efficacy of a new antibody (T10B9.1A-31) in preventing rejection of transplanted kidneys. The researchers are comparing their new antibody to the efficacy of an antibody known as OKT3, whose rejection-preventing efficacy has already been established. In the first 59 patients T10B9.1A-31 was at least as effective as OKT3 in reversing acute renal allograft rejection. In addition, T10B9.1A-31 offers several significant advantages over OKT3 therapy. First, T10B9.1A-31 administration is characterized by a more rapid decrease in creatinine, a serum substance associated with kidney failure. Second, Tl0B9.1A-31 administration results in fewer and less severe first-dose and later side effects. The efficacy of both these antibodies is diminished when the body mounts an immune response against them, but this immune response is less likely to develop against T10B9.1A-31 than OKT3, and the type of immune response against T10B9.1A-31 is such that use of OKT3 is still possible. Finally, T10B9.1A-31 therapy is associated with fewer infections than OKT3 therapy.

Reproduction

Testing Potential Male Contraceptives. Synthetic analogs of gonadotropin-releasing hormone (GnRH), known as GnRH antagonists, are being studied extensively as potential male contraceptives. Released by the hypothalamus in the brain, GnRH stimulates the secretion of gonadotropins by the neighboring pituitary gland. Gonadotropins are hormones that are required for sperm production and manufacture of the male sex hormone testosterone by the testes. GCRC investigators at the Harbor-University of California, Los Angeles, Medical Center have tested a potent GnRH antagonist called Nal-Glu for its ability to suppress sperm production. They administered Nal-Glu subcutaneously daily to eight normal men for 16 weeks. To prevent impotence, the men also received supplements of testosterone. Seven of the eight men produced no sperm 6 to 8 weeks after treatment began, but sperm counts returned to baseline values 10 to 12 weeks after the last Nal-Glu injection. Libido and sexual function were normal during testosterone replacement and recovery periods. These results demonstrate that a combination of a potent GnRH antagonist and testosterone can predictably and reversibly block sperm production while maintaining libido and sexual function.

Skin Diseases

Cyclosporine Treatment of Psoriasis. GCRC investigators at the University of Michigan Medical Center in Ann Arbor have found that the immunosuppressive drug cyclosporine has a dramatic effect against psoriasis. They treated 85 patients who had severe or disabling psoriasis with cyclosporine in three different doses. The patients were randomly assigned to receive one of the cyclosporine doses or a placebo. The 4-month study showed that cyclosporine treatment improved psoriasis in a dose-dependent fashion. Corresponding to the three increasing doses of cyclosporine, 36, 65, and 80 percent of the patients in the respective groups were clear or almost clear of psoriasis. However, kidney function, measured as glomerular filtration rate (GFR), decreased by a median of 16 percent in all patients receiving cyclosporine. Although GFR returned toward normal after cessation of cyclosporine therapy, kidney function remains the major concern. This study and other demonstrations of cyclosporine's effect against psoriasis provide new hope for patients with this debilitating disease.

Biomedical Research Technology Program

Program Description

The Biomedical Research Technology Program (BRTP) supports and promotes the development and use of leading-edge technologies by the biomedical research community. At the 62 BRTP-funded resource centers across the country scientists have access to expensive state-of-the-art equipment and also receive the necessary training to utilize these sophisticated instruments to their full potential. The current emphasis of the program is on extending the biomedical applications of computers, engineering new instruments to solve biomedical problems, and advancing the study of molecular and cellular structure and function through application of specialized technologies.

In FY 1992 the NCRR provided $46.3 million for the BRTP, approximately $37 million of which was spent in support of the resource centers. Each center functions as a national or regional resource for the biomedical research community and offers advanced equipment and technologies that are among the best in the world. Staff scientists at the resource centers collaborate with outside biomedical investigators to solve research problems using the technologies of the resource. Among the available instruments are high- and intermediate-voltage electron microscopes; advanced laser instrumentation; mass spectrometers; magnetic resonance spectrometers; x-ray diffraction and detection instruments; and a variety of computer systems for modeling molecular interactions and disease progression, image analysis, and supercomputing.

In addition to providing funds for resource centers, BRTP funds Pre-Resource Research Grants. These are used to develop technologies or instruments that in the future can be incorporated into new, user-oriented resource centers. The focus of the Resource Center Grants, Pre-Resource Research Grants, and the newly instituted R01 program is unique to BRTP. Unlike other institutes, the emphasis in BRTP is on research and development of new technologies or instruments with broad biomedical applications, rather than applications to specific diseases. For small-scale, high-risk projects, BRTP provides funds through its Small Grants for Innovative Technology to stimulate the development of new, unproved equipment and procedures.

Other types of funding available from BRTP include Small Business Innovative Research Grants for research on potentially marketable products and First Independent Research Support and Transition Awards, which provide initial support to newly independent biomedical investigators. The BRTP is also authorized to award conference grants, cooperative agreements, and contracts to carry out its mission.

Promoting communication within the biomedical research community is an important component of the BRTP's objectives. Through publications, seminars, workshops, and conferences BRTP grantees disseminate research achievements and announce training opportunities and the availability of technical information in the resource centers.

Research Highlights

Advanced Computer and Communication Systems

High-Performance Computing Research: A National Agenda. In recent years the increased availability of high-performance computers has contributed greatly to biomedical research in areas such as structural biology, neuroscience, and cell biology. Support for this technology is receiving a significant boost from a government-wide initiative on high-performance computing and communications, promoted under the auspices of the White House Office of Science and Technology Policy. The BRTP plays a major role in NIH participation in this initiative, supporting four resource centers that apply high-performance computing techniques to a variety of cutting-edge biomedical research problems. These resource centers give the biomedical research community access to the latest, most powerful computer technology and complementary software and algorithms for efficient, effective performance.

In FY 1992 a new resource center was added to the BRTP roster: the Parallel Processing Resource for Biomedical Scientists at Cornell University, cofunded by the National Science Foundation. This new center addresses biomedical problems too complex to be solved by

Dr. Klaus Schulten demonstrates the 60-node parallel supercomputer at the Resource for Concurrent Biological Computing at the University of Illinois, Urbana. Employing the power of massively parallel computing, he and his colleagues have modeled the action of an enzyme that plays a key role in asthma, arthritis, and toxic shock syndrome.

Thompson-McClellan Photography

experimentation on existing mainframe computers. Along with the other three BRTP-funded high-performance computer resources—the Supercomputing Resource for the Biomedical Community at the Pittsburgh Supercomputing Center in Pennsylvania; the Resource for Concurrent Biological Computing at the University of Illinois, Urbana; and the Theoretical Simulation of Biological Systems Resource at Columbia University in New York City—the Cornell center will tackle such problems as protein folding, drug design, and simulations of large and complex biological systems. At present, high-performance computing offers the only opportunity for solving problems of this complexity.

Technologies for the Future. Because advanced computer systems promise to play a prominent role in biomedical research in the coming years, the BRTP sponsored a 2-day workshop titled "Technologies for the Future: Biomedical Computing for Visualization, Modeling, and Decision Support." Experts in the field of biomedical computing gathered to explore the need for and the potential of high-performance computing, particularly in the emerging area of massively parallel computer architecture. Workshop participants examined possible applications of modeling and simulation programs, decision support in biomedical experimentation, and other evolving technologies. A report of their findings and recommendations is currently in press.

Modeling Enzyme Action in a Cellular Membrane. The small lipid-digesting enzyme known as phospholipase A2 plays a key role in defending the body against bacteria. But when this enzyme is out of control it contributes to the inflammation of tissues in asthma, arthritis, and toxic shock syndrome. Hoping to develop inhibitors that prevent phospholipase A2 overactivity, some researchers have turned to computer modeling to learn more about how the enzyme may function in its natural environment—bound to a cellular membrane and surrounded by water molecules.

In one of the largest and longest computer simulations of biological macromolecules performed to date, scientists at the Resource for Concurrent Biological Computing at the University of Illinois, Urbana, have modeled the structure of a bilipid biological membrane and studied the action of phospholipase A2 in this environment. To do this the researchers developed programming techniques that exploit the power of a new generation of massively parallel computers, allowing them to model very large molecular ensembles that are beyond the scope of programs used in conventional supercomputers. In collaboration with investigators at Eli Lilly, the BRTP-supported scientists identified the interactions that govern how the enzyme binds to a layer of lipids. The researchers have now moved into the next phase, modeling the action of the enzyme and the role of enzyme inhibitors.

Genetic Susceptibility to Lung Cancer. With the aid of computers and novel statistical software for genetic analysis, scientists at the BRTP-supported Resource for Human Genetic Analysis at Louisiana State University Medical Center in New Orleans found further evidence that susceptibility to lung cancer is inherited. The researchers studied 337 Louisiana families (a total of 4,357 people) in which at least one member had died of lung cancer. Among families in which this lung cancer victim was born before World War I, most early onset cases of lung cancer seemed to be triggered by a combination of smoking and the presence of a major lung cancer gene. In contrast, among families in which the lung cancer victim was born after World War I, when cigarette consumption dramatically increased, the best fitting genetic model implied that virtually all lung cancers occurred among carriers of the putative gene. Because these gene carriers rarely developed lung cancer if they were not exposed to tobacco smoke, this model suggests that the disease does not arise from genetic factors alone but from a combination of the effects of the gene and the environment.

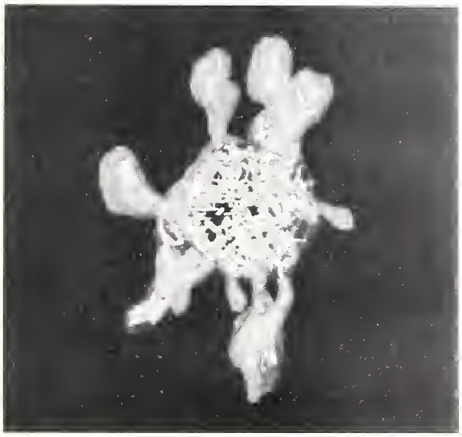
In a separate analysis of the same data, the scientists found that 77 percent of the nonsmokers who developed lung cancer were female, which may indicate that a major gene has a greater cancer-causing influence in women than in men. Pilot studies cofunded by BRTP and the new NIH Office of Research on Women's Health are now under way to determine the extent that genetic factors contribute to lung cancer in both sexes.

Communication Networks Link Distant Instruments. The cumbersome processes of submitting a research proposal, scheduling time, and then traveling to a distant site to use a higher voltage electron microscope is enough to keep many biologists from using these powerful and expensive instruments. But in the not-too-distant future scientists may tap into the power of expensive intermediate-voltage or high-voltage microscopes without leaving their laboratories. This is the concept of a "distributed laboratory," designed to connect widely separated national resources via a high-speed communication network, thereby saving traveling time and making expensive instruments more accessible to the scientific community.

In a pioneering experiment at a meeting in Chicago, Illinois, scientists demonstrated the potential of the distributed laboratory by operating a 400-kilovolt electron microscope that was 1,700 miles away, housed at the BRTP-funded San Diego Microscopy and Imaging Resource (SDMIR) at the University of California, San Diego. This is one of only eight higher voltage electron microscopes available to U.S. biologists. Greater access to these limited resources could be a real boon to structural biologists. These eight microscopes—seven of them supported by BRTP—can analyze thicker specimens and provide more three-dimensional information than can a standard 100,000-volt electron microscope.

In the prototype experiment an operator at the SDMIR loaded the specimen and focused the microscope, and scientists in Chicago operated the Microscopist's Workstation, which controlled other functions such as specimen position and magnification. Image information was communicated by a fiber-optic data link from the microscope to the National Science Foundation's San Diego Supercomputer Center, where the data were processed and then transmitted to the workstation in Chicago. There researchers viewed 3-D animations and stereo images that showed depth perspective.

The Microscopist's Workstation was developed by scientists at SDMIR, the San Diego Supercomputer Center, and the Scripps Research Institute in La Jolla, California. The investigators are now planning to link their high-powered microscope to laboratories in at least two other states, and software under development will enable investigators to access the microscope using simpler computer workstations.



At the San Diego Microscopy and Imaging Resource scientists are developing improved techniques for visualizing subcellular structures—such as the Golgi apparatus or endoplasmic reticulum—in three dimensions. Shown here is a branching portion of a neuron, reconstructed to show the smooth endoplasmic reticulum in light gray. The cell membrane, which has been rendered transparent, is shown in darker gray.

Maryann Martone, David Hessler, and Mark Ellisman, University of California, San Diego

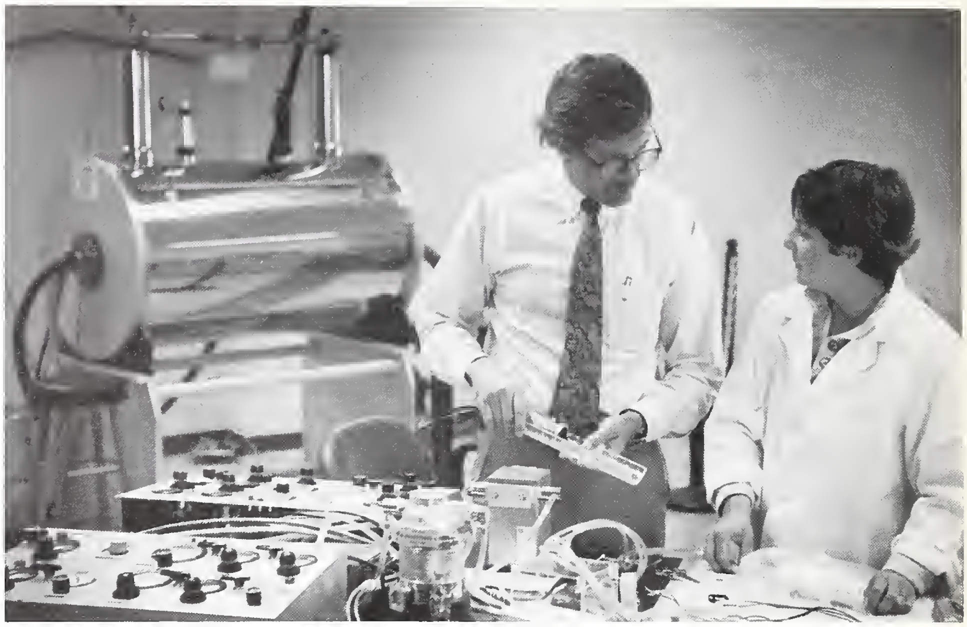
Analysis of Large Biomolecules

Structural Studies of Gangliosides in Nerve Cell Tumors. Gangliosides are cell-surface molecules that several types of tumors shed readily into the circulatory system. By elucidating the structure and function of these molecules, researchers hope to better understand—and even alter—the process of tumor formation and progression.

For more than a decade investigators at the BRTP-funded Mass Spectrometry Facility at Michigan State University (MSU) have collaborated with scientists at the University of California, Los Angeles, School of Medicine and Children's National Medical Center in Washington, DC, to purify and analyze the fine structure of several types of gangliosides found in association with neuroblastomas, highly invasive tumors of the sympathetic nervous system. Neuroblastoma is the most common solid, malignant tumor of childhood and infancy, and one of the most deadly.

Because only tiny amounts of gangliosides can be isolated from tumor cells, the detailed structure of these molecules has remained elusive until recently. Using the technology at the MSU resource, however, the collaborating investigators are able to analyze infinitesimally small quantities of gangliosides. Already they have discovered several new structures that had not been known to exist in neuroblastomas.

Further study at the Children's National Medical Center revealed that at least 10 types of ganglioside molecules are immunosuppressive, and a clinical investigation found that high blood levels of gangliosides in children with neuroblastomas correlated with a poorer



The BRTP-supported Center for In Vivo Microscopy at Duke University Medical Center, Durham, North Carolina, boasts a wide array of instruments for high-resolution, three-dimensional NMR imaging of tissues. Here the center's director Dr. G. Allan Johnson and Dr. Helene Benveniste use proton MRI to study the early stages of stroke in rats.

Jim Wallace, Duke University

clinical outcome. The scientists speculate that shed gangliosides may protect tumor cells from destruction by suppressing the action of T-cells and the immune system, thus ultimately promoting tumor progression. The investigators are now working to characterize more complex ganglioside structures using a technique called electrospray mass spectrometry.

Interactions Between Cholera Toxin and the Cell. *Vibrio cholerae*, the bacterium that causes cholera, secretes a protein that is toxic to humans. Scientists at the BRTP-supported Biocalorimetry Center at Johns Hopkins University in Baltimore, Maryland, have focused their attention on how this toxin binds to the surface of the cell and the forces that drive this interaction.

Using sensitive techniques such as isothermal titration calorimetry and high-sensitivity differential scanning calorimetry, the researchers studied how one subunit of the toxin may fold and change when it binds to the cell-surface receptor known as GM1-ganglioside. The binding of the subunit to the receptor triggers a series of events that result in a second toxic subunit penetrating the cell membrane.

In recent experiments the BRTP-supported investigators collaborated with scientists at the University of Milan, Italy, to show that an alternative form of the ganglioside also binds to cholera toxin. Using ultrasensitive isothermal titration calorimetry, the researchers found that the energetics of this interaction are remarkably similar to those seen when GM1-ganglioside binds to the toxin. If this alternative receptor is present in the intestinal mucosa, where *Vibrio cholerae* tends to congregate and wreak havoc on the body's water balance, it could play an important role in the progression of the disease.

Comparative Medicine Program

Program Description

Laboratory animals continue to have a prominent role in biomedical research. Nearly one-half of the research projects supported by the National Institutes of Health include the use of animals, and most of the important medical advances during the past 100 years can be attributed, at least in part, to the use of laboratory animals.

The Comparative Medicine Program (CMP) provides support for laboratory animal resources and related research projects that are essential for biomedical research. The three major areas of the CMP are the Regional Primate Research Centers Program, the Laboratory Animal Sciences Program, and the AIDS Animal Models Program.

During FY 1992, the CMP received a total allocation of $72.4 million. These funds were used to support core resource and research activities at the seven Regional Primate Research Centers; identify and develop new and improved animal models for important human diseases; improve the health and well-being of laboratory animals through research on intercurrent diseases, diagnostic services, psychosocial behavioral studies, and psychological behavioral studies, as well as by improving their housing and environmental conditions; breed and enhance colonies of scarce animal species that are useful in biomedical research, including AIDS-related investigations; and provide knowledge concerning the optimal care and use of laboratory animals.

The seven Regional Primate Research Centers received a total allocation of $41.3 million for their core activities in FY 1992. The research resources of these centers are available for use by qualified biomedical investigators on a regional and national basis.

The many and varied activities supported by the Laboratory Animal Sciences Program (LASP) received a total budget allocation of $22.3 million in FY 1992. The LASP encompasses research and resources to improve the health and overall quality of laboratory animals; studies of methods to control or prevent diseases of laboratory animals; and development, characterization, and improvement of animal models for human diseases.

The AIDS Animal Models Program supports resources that identify, develop, and make available appropriate animal models for AIDS-related research. This program received a total budget allocation of $8.8 million in FY 1992 to sponsor the National Chimpanzee Breeding and Research Program and the Specific-Pathogen-Free Macaque Breeding and Research Program to provide primates for Public Health Service-sponsored basic and clinical research on AIDS.

Regional Primate Research Centers Program

The seven Regional Primate Research Centers are a unique national network of nonhuman primate research and resource facilities established in the early 1960's. Nonhuman primates are vital links between basic research and applications in humans. Often particular medical or behavioral questions can be studied only in these animals. Through the shared resources of the seven centers NIH provides cost-effective national repositories of primates, scientific expertise, and specialized facilities and equipment necessary for biomedical research on primates.

The seven centers and the host institutions with which they have close administrative and research relationships are:

- **California Regional Primate Research Center,** Davis, associated with the University of California at Davis;
- **New England Regional Primate Research Center,** Southborough, Massachusetts, associated with Harvard University, Cambridge;
- **Oregon Regional Primate Research Center,** Beaverton, associated with the Medical Research Foundation of Oregon, Portland;
- **Tulane Regional Primate Research Center,** Covington, Louisiana, associated with Tulane University, New Orleans;
- **Washington Regional Primate Research Center,** Seattle, associated with the University of Washington, Seattle;

A chimpanzee plays with her offspring at the Yerkes Regional Primate Research Center in Atlanta, Georgia, the only one of the seven Regional Primate Research Centers with a colony of great apes.

Courtesy of Yerkes Regional Primate Research Center

- **Wisconsin Regional Primate Research Center,** Madison, associated with the University of Wisconsin, Madison;
- **Yerkes Regional Primate Research Center,** Atlanta, Georgia, associated with Emory University, Atlanta.

Each of the seven Regional Primate Research Centers has close administrative and research relationships with its host institution. The centers provide the basic elements necessary for primate research for over 1,200 U.S. scientists whose scientific missions serve all the categorical institutes of NIH as well as other government, private, and commercial agencies that support biomedical research. These scientists represent 383 different research institutions. In addition to serving investigators on site, the centers' tissue distribution programs provide more than 13,000 specimens per year to laboratories throughout the country. In total, the centers provide access to more than 17,000 nonhuman primates, representing 32 species, that have been found valuable for basic biological and medical research. Many of the animals are in breeding colonies that are essential to our nation's biomedical research needs and represent an irreplaceable national resource.

Laboratory Animal Sciences Program

The Laboratory Animal Sciences Program provides grants to support research, develop research animal resources, and train research scientists in the field of comparative medicine. The program elements of the LASP are:

Research. The LASP supports basic and applied research in comparative medicine, particularly in the areas of laboratory animal science, laboratory animal medicine, and comparative pathology that do not fall within the categorical interest of a single NIH institute. The research supported encompasses:

- Biotechnology: Improvement of transgenic technology, cryopreservation methods, and reproductive performance.
- Normative biology: Animal genetics, animal behavior, identification and characterization of nontraditional species for research, animal nutrition, and reproductive physiology.
- Animal disease: Detection and characterization of diseases that interfere with research and threaten animal welfare, vaccine development, and development of animals genetically resistant to disease.
- Animal welfare: Improved methods for evaluating and alleviating pain, distress, and discomfort; development of environmental enrichment; and improved housing and husbandry technology.
- Animal models: Continued discovery and development of natural and induced animal models for human biology and disease.

The LASP sponsored 26 research projects during this period through awards that included Investigator-Initiated Research Projects (R01), Small Research Grants (R03), Resource-Related Research Projects (R24), First Independent Research Support and Transition (FIRST) Awards (R29), and Small Business Innovation Research Grants (R43/44).

Training and Career Development. The goal of LASP-supported training is to produce graduates with the research skills, clinical training, and motivation to become career participants in biomedical and health research. A central theme in this training is building a basic core of knowledge in comparative medicine, particularly in such areas as laboratory animal medicine and comparative pathology. In FY 1992 LASP supported the training of 73 veterinarians through National Research Service Awards (NRSA) at 16 institutions. In addition, five veterinarians received individual NRSA postdoctoral awards, and eight predoctoral students received NRSA short-term research training awards.

LASP also continued the Special Emphasis Research Career Award (SERCA) program and supported 12 SERCA awards during FY 1992. SERCA awards are made to veterinarians to assist their development in biomedical research careers involving the use of laboratory animals.

Diagnostic and Investigative Laboratories. This year, as a result of a major program decision, support began to be phased out for diagnostic and investigative laboratories (DIL's). Comparative Medicine Research Program Project (P01) awards will replace DIL's. These awards are described below. Fourteen DIL's are currently being supported with Animal Resource Grants (P40). They have provided major resources for laboratory animal diagnostic service, research, and training at institutions receiving significant NIH funding. These institutional diagnostic services are important. However, the P01 program will focus on research and diagnostic service needs and will necessarily derive support from other sources. Of the 14 current DIL projects, 8 will be phased out during FY 1992 and FY 1993. The remaining six DIL projects will be phased out in succeeding years.

Comparative Medicine Research Program Projects. LASP announced the new Comparative Medicine Research Program Project (CMRPP, P01) award program this year. As noted above, this program will replace the existing DIL program. The overall objective of a CMRPP is to establish an environment that will enhance scientifically meritorious and productive research, encourage collaboration, and provide a setting conducive to advanced research training. Each CMRPP will consist of at least three and no more than six research projects that are under the leadership of an experienced investigator and conducted in areas that are relevant to LASP interests. In addition, a core unit will be supported to provide common laboratory, clinical, and administrative services. A maximum of $432,000 (direct costs) will be awarded annually for up to 5 years. Interest in this new program has been widespread and a number of P01 applications have been received for consideration during FY 1993.

Animal Model Development and Special Resources. Animals develop a number of natural diseases that are very similar to human diseases. Bacterial and viral infectious diseases, endocrine abnormalities, inherited metabolic disorders, and tumors are among the maladies that are shared between animals and humans. Animals therefore often provide excellent models for the study of diseases that afflict humans.

During FY 1992 LASP supported four animal model development and special colony projects. These projects were devoted to identifying new models for human disease and

Studies of rhesus monkeys at Yerkes Regional Primate Research Center in Atlanta, Georgia, helped Dr. Bernard McCarey to develop and test hydrogel lens implants, which are now being evaluated in clinical trials. The implants may benefit elderly patients who have had cataract surgery but cannot wear eye glasses or contact lenses to correct vision problems.

Courtesy of Yerkes Regional Primate Research Center improving and further characterizing already identified models. They also increased the availability of animal models that have proved useful to biomedical researchers but are unavailable through commercial sources. LASP also proposed a new initiative for the preservation of animal models that was endorsed by the National Advisory Research Resources Council. This initiative will provide a long-term, stable, integrated program for safeguarding national research animal resources of importance to projects sponsored by the Public Health Service.

The Cryopreserved Mouse Embryo Repository at the Jackson Laboratory in Bar Harbor, Maine, represents a resource of this type. This center has pioneered the techniques used for freezing mouse embryos to preserve valuable strains that may be needed for later research use.

Primate Resources. LASP supported several projects related to the breeding, genetic characterization, and enzootic diseases of nonhuman primates used in research.

The Caribbean Primate Research Center (CPRC) of the University of Puerto Rico has a large colony of rhesus monkeys and several smaller colonies of other species of nonhuman primates. Maternal, genealogical, and demographic data have been collected continuously on the free-ranging rhesus monkey colony on the offshore island of Cayo Santiago since 1956. This has resulted in the most complete life history information on any nonhuman primate population in the world. The CPRC also maintains over 2,000 complete nonhuman primate skeletons for research. Approximately 900 of the skeletons are of known identity, age, sex, matriline, social group, diet, and reproductive history. The skeletons are valuable for studying normal and abnormal skeletal development, the effects of different diets, and the differences between sexes. The colonies support a wide variety of research studies including studies on obesity, diabetes mellitus, hypertension, pathology of joints and bones, ocular diseases, and AIDS.

Support is also provided for the largest breeding colony of squirrel monkeys in the United States. This colony is at the University of South Alabama in Mobile. Behavioral, biochemical, and cytogenetic studies are carried out, in addition to breeding, to optimize the reproductive efficiency of the colony and to make the squirrel monkey a better animal model for use in research. A LASP-sponsored project to enhance B-virus diagnosis and control in primate colonies has been instrumental in monitoring the prevalence of B-virus infections. This research continues to be directed toward developing better serological and B-virus antigen detection tests that will facilitate diagnostic and prevalence studies.

Reference and Information Centers. Activities supported by LASP in this area include registries, reference centers, and publication of newsletters and other information sources related to laboratory animals. Four projects were supported during 1992. The Registry of Comparative Pathology at the Armed Forces Institute of Pathology in Washington, DC, maintains a collection of tissues and illustrative material that is available for research and research training. It conducts workshops, symposia, and short courses and prepares study sets and syllabi for loan. The registry also publishes the *Comparative Pathology Bulletin* and the diagnostic exercise feature that appears in *Laboratory Animal Science*.

The Institute of Laboratory Animal Resources of the National Research Council, with the support of LASP and other Government agencies, provides scientific and technical information concerning laboratory animal resources. It develops guidelines on laboratory animal care and use and conducts workshops on laboratory animal problems.

The *Laboratory Primate Newsletter* at Brown University and the *New Listings* from the Primate Supply Information Clearinghouse at the University of Washington, Seattle, provide important information about the care, breeding, and supply of nonhuman primates for laboratory studies. These publications provide valuable information to research primatologists, since the use of nonhuman primates is increasing but the supply of available animals is dwindling.

Institutional Animal Facility Improvement. Healthy research animals are essential for obtaining meaningful and reproducible experimental data. To assist institutions in their efforts to meet the animal care guidelines and policies established by the Public Health Service, as well as the Animal Welfare Act requirements, LASP has continued to support projects to improve institutional animal facilities. In FY 1992 48 animal resource improvement applications were funded at a total of approximately $8.5 million. This support was used to renovate laboratory animal facilities, enhance the environmental conditions of laboratory animals, upgrade animal caging, and improve sanitation equipment such as cage washers and autoclaves.

Conference Support. LASP supports conferences that are directed toward consolidating and advancing the body of knowledge related to comparative medicine. During FY 1992 LASP supported three conferences in these areas: Definition, nomenclature, and conservation of rat strains; primate reproduction; and nonhuman primate models for AIDS.

AIDS Animal Models Program

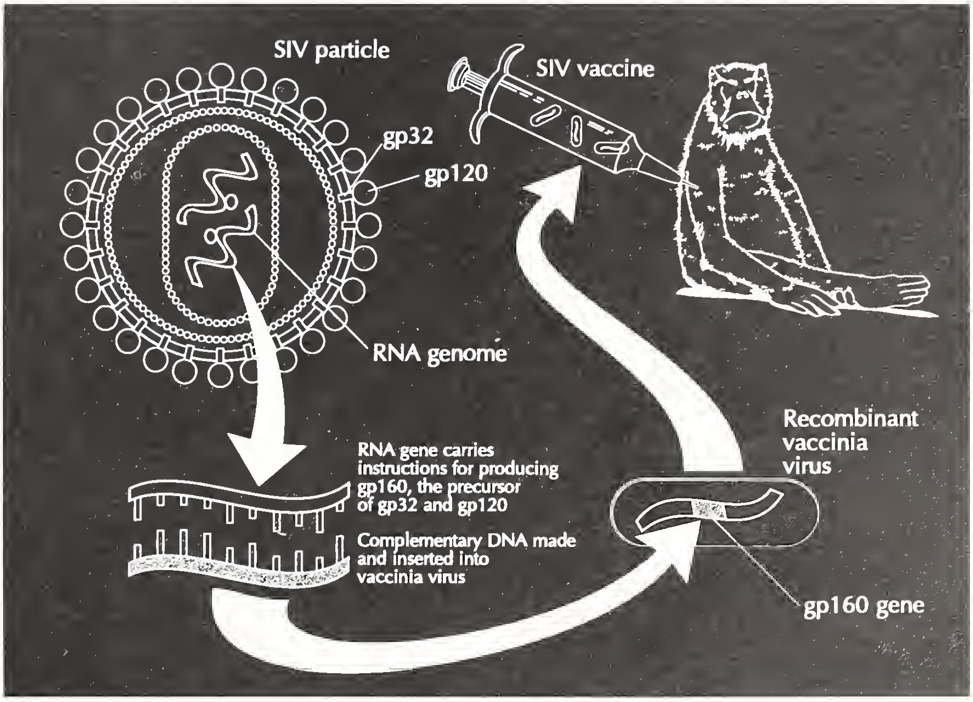
The AIDS Animal Models Program promotes the characterization and validation of existing models, expands development of new models, and coordinates these common interests with other NIH institutes.

Basic and clinical research on AIDS-related diseases has been greatly accelerated by the development of nonhuman primate models that are susceptible to human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection and show, both serologically and clinically, the symptoms observed in human AIDS. It is now possible to conduct basic research on AIDS in nonhuman primate models with a high degree of confidence that the studies are directly applicable to the human syndrome.

Chimpanzee Breeding and Research Program. The Chimpanzee Breeding and Research Program (CBRP) is the first and only national program to combine the expertise and experience of both chimpanzee breeders and researchers. The CBRP provides the Public Health Service-supported biomedical research community with an adequate supply of chimpanzees for investigations of important human health problems, including viral hepatitis and AIDS. The AIDS Animal Models Program administers this important resource, and the CBRP Management Committee provides oversight and advice. The committee develops policies related to a wide range of issues, including use of chimpanzees in infectious disease research, safety considerations for personnel working with chimpanzees, and environmental enrichment for the captive population. There are currently 505 disease-free adult breeding chimpanzees in the program's colonies, and 302 offspring have been produced since the inception of the program in 1986. Forty-five percent of these offspring are mother-reared; the remainder are reared with other young chimpanzees in nursery-type environments. By design, the CBRP population growth rate has now been stabilized to maintain the population.

Research projects integrated into the breeding program are conducted to correct gaps in scientific knowledge and problems affecting the reproduction of chimpanzees in captive environments. The projects focus primarily on behavioral development, reproduction, genetics, health, demography, and breeding management. These studies are conducted at the University of Texas M. D. Anderson Science Park at Bastrop; the Primate Foundation of Arizona in Tempe; the University of Southwestern Louisiana's New Iberia Research Center; the Yerkes Regional Primate Research Center in Atlanta, Georgia; the New Mexico State University Primate Research Laboratory at Holloman Air Force Base; the International Species Information System in Apple Valley, Minnesota; and the Nonhuman Primate Genetics Typing Laboratory at Trinity University in San Antonio, Texas.

Intense efforts are made to ensure that chimpanzees are used in the most appropriate and humane manner when employed as a research model. Chimpanzees from the CBRP may be assigned to U.S. Public Health Service or other Government-supported research


SIV particle
SIV vaccine
gp32
gp120
RNA genome
RNA gene carries instructions for producing gp160, the precursor of gp32 and gp120
Complementary DNA made and inserted into vaccinia virus
Recombinant vaccinia virus
gp160 gene

A recombinant AIDS vaccine tested at the Washington Regional Primate Research Center in Seattle completely protected macaques from infection with simian immunodeficiency virus (SIV), which causes an AIDS-like disease in monkeys. The vaccine was produced by isolating pieces of DNA that carry instructions for manufacturing the SIV protein known as gp160. Scientists inserted the gp160 gene into a harmless virus to produce the recombinant vaccine. The researchers are now testing this vaccine under a variety of conditions to determine if broad protection against a range of SIV subtypes can be achieved.

The CMP-funded B Virus Diagnostic Resource and Reference Laboratory in San Antonio, Texas, provides rapid identification of Herpesvirus simiae *(B virus) in blood and other tissue samples from humans and nonhuman primates. B virus produces mild symptoms in macaques but can be fatal to humans. Here research assistant Henry T. Sentmore III follows strict biocontainment procedures as he prepares to study autopsy specimens from a person who died of B virus infection.*

Dennis Havel, Southwest Foundation for Biomedical Research

projects only after the research protocols have been approved by the Interagency Animal Models Committee. This review is in addition to prior evaluations of the individual protocols by the respective Institutional Animal Care and Use Committees and the funding agency's peer review system.

Specific-Pathogen-Free Macaque Breeding and Research Program. SIV research in macaques is of critical importance to the concerted AIDS research effort. The Comparative Medicine Program's specific-pathogen-free (SPF) macaque breeding colonies are currently in their fifth year of development. Characterization and demographic status of the SPF colonies have been determined, and it is now possible to estimate the production rate over the next 5 to 6 years. Expert retrovirologists recognize that an adequate, dependable supply of high-quality SPF macaque monkeys is absolutely essential for future AIDS-related investigations. The recent finding that the pig-tailed macaque, *Macaca nemestrina*—a close relative of the rhesus macaque—can be infected with HIV-1 is potentially a major scientific advance. However, additional research will be required to confirm its value as a model for human HIV-1 infection and AIDS. To facilitate these studies the SPF Breeding and Research Program will incorporate a limited number of pig-tailed macaques into the breeding program.

To ensure that SPF macaque monkeys are available for AIDS research, breeding colonies have been established at the Texas Primate Center of Hazleton Research Products in Alice; the New England Regional Primate Research Center in Southborough, Massachusetts; the University of Texas M. D. Anderson Science Park at Bastrop; the Michigan Department of Public Health in Lansing; the Laboratory Animal Breeders Service in Yemassee, South Carolina; and the University of Miami School of Medicine in collaboration with Charles River Laboratories, Key Lois, Florida.

These program centers have established their primary core breeding colonies and are currently producing offspring. The combined SPF colonies total over 1,500 animals, with the number of breeding females representing 45 percent of the total population. To promote continuing buildup of the colonies all female offspring will be returned to the colonies for breeding during the next 2 to 3 years. Most of the colony's young males and retired breeders are currently available for AIDS-related research, with priority given to projects sponsored by the U.S. Public Health Service.

The breeding facilities have been furnished with modern caging equipment, and innovative long-term holding areas for the colonies are in place. In addition to the production aspects of making SPF animals available for biomedical research, the SPF program promotes research projects for the enhancement of well-characterized and healthy animals through the development of modern diagnostic tests; improved housing and innovative husbandry practices; computerized record keeping systems; and new techniques that permit indepth genetic monitoring.

Companion research activities in virology, genetics, and behavioral enrichment play a major role in support of program goals. Virology reference laboratories perform tests to prevent and control herpes B virus and simian retrovirus infections, participate in basic viral research, and provide strategies for ongoing colony production. Together these laboratories have performed more than 9,000 tests to ensure the SPF status of the colony animals. The Herpes B Virus Laboratory of the Southwest Foundation for Biomedical Research in San Antonio, Texas, provides rapid virological and serological screening and identification of possible *Herpesvirus simiae B* infection.

The Simian Retrovirus Reference Laboratory at the University of California Regional Primate Research Center in Davis focuses on identification and control of simian retroviruses in captive nonhuman primate populations, with particular emphasis on the SPF breeding colonies.

The Primate Genetics Reference Laboratory at the California Regional Primate Research Center provides the SPF colonies with genetic information to enhance breeding potential. The current emphasis is to correlate genealogical relationships within the SPF colonies with behavioral and biomedical data; to monitor the genetic structure of breeding groups; and to recommend strategies to maintain genetic diversity and minimize inbreeding.

Research Highlights

Regional Primate Research Centers

Potential New Animal Model for AIDS. Investigators at the Washington Regional Primate Research Center (WRPRC) have reported the first successful studies demonstrating infection of the pig-tailed macaque monkey *(Macaca nemestrina)* with HIV-1.

The WRPRC researchers evaluated *M. nemestrina* as a model for HIV-1 infection because clinical and virological observations suggested that this species was more severely

The pig-tailed macaque may prove to be a valuable research animal in the study of AIDS and potential vaccines. Scientists at the Washington Regional Primate Research Center in Seattle report that pig-tailed monkeys are susceptible to infection by HIV-1, the most prevalent type of human AIDS virus, whereas other monkey species are not.

Martin Mauer, Washington Regional Primate Research Center

affected by SIV and HIV-2 infection than were *Macaca mulatta* or *Macaca fascicularis*, the monkeys most commonly used in AIDS research. Their studies showed that peripheral blood mononuclear cells (PBMC) from *M. nemestrina* were susceptible to infection by several HIV-1 strains in vitro. Further, in three separate experiments eight *M. nemestrina* that had been inoculated with HIV-1 developed antibody against the virus, and HIV-1 infection of PBMC was demonstrated. These results suggest that *M. nemestrina* should be a useful animal model for studying acute HIV-1 infection and evaluating infection-blocking abilities of vaccines and therapies.

Genetically Attenuated Vaccine Prevents Simian AIDS. Researchers at the New England Regional Primate Research Center have developed a vaccine that provides complete, long-term protection against SIV. The vaccine is based on live simian AIDS virus that has been weakened by genetic manipulation (gene deletion). The six rhesus monkeys that were vaccinated have remained healthy for over 3 years, even after exposure to varying doses of wild-type, pathogenic SIV more than a year ago. Earlier SIV vaccines—whether subunit vaccines or vaccines based on whole, killed virus—have been unable to protect monkeys against challenge with different or uncloned strains of SIV. This type of vaccine may soon be tested in high-risk human volunteers, although extensive safety testing might take a decade or more.

Mouse Study May Help AIDS Research in Humans. Lentiviruses are a subfamily of retroviruses, which are responsible for a wide variety of animal and human diseases. HIV and the related SIV are among the best known. Lentiviruses cause disease in horses, sheep, goats, cattle, and cats, but detecting these viruses can be difficult. LASP-supported researchers at Rockefeller University have developed a diagnostic probe based on the highly sensitive polymerase chain reaction. This work was based on initial research on mouse T-cell depletion by viruses and has now been used to detect lentiviruses in a variety of species.

Glycogen Storage Disease Type IV in the Norwegian Forest Cat. The Referral Center for Animal Models of Human Disease at the University of Pennsylvania has identified a family of purebred cats with glycogen storage disease type IV (GSD IV, Anderson disease). The human homolog of this disease causes fatal liver, cardiac, and neural pathology within 1 to 2 years of life due to the deficiency of a particular glycogen branching enzyme. No animal model has previously been available for studying new therapeutic methods for GSD in humans. The disorder is inherited as an autosomal recessive trait and lack of the enzyme results in storage of abnormal glycogen in skeletal, cardiac, and smooth muscle; liver; neurons; and cells of the reticuloendothelial system. Enzyme activity in the liver and skeletal muscle of affected cats was tenfold to twentyfold less than in normal cats, and the parents of affected cats have about one-half the normal enzyme activity. To produce more kittens for study, the center has established a breeding colony. To date, 6 of 19 kittens have been born with the disease, but unfortunately died neonatally. These kittens showed defects typical of the disease. Two female kittens that may be affected have survived to 4 months of age. Efforts are continuing to further define the enzyme deficiency and to evaluate feline GSD IV as a model for the human disease.

Fish Used as Human Disease Models. Research on fish as a model for Wilson's disease (a copper storage disease) is continuing in the diagnostic and investigative laboratory resource at the Johns Hopkins University School of Medicine in Baltimore, Maryland, to further characterize cellular and subcellular components of the developing fish liver. This work is being done in conjunction with development of aquatic bioassays that use fish as an alternative to mammals for carcinogenicity and toxicity testing and health risk assessment. Aquatic bioassays are of interest because of the abundance, relative availability, low maintenance and housing requirements of many fish species, as well as possible lower costs than rodent bioassays. Many characteristics of tumor development in fish in response to carcinogens are similar to those seen in rodents in test situations and in fish in contaminated environments. The medaka *(Oryzias latipes)* has emerged as one of the primary species used in fish bioassays. In the past year modified immunohistochemical techniques have been applied to assist in tumor diagnosis. Antibodies against keratin, desmin, and glial fibrillary acidic protein have shown promise. These and other untested reagents will assist in the diagnosis of tumors in aquatic bioassays and a better understanding of the makeup of cellular components of the liver in fish.

Implanted Chamber Improves Antibody Production Technique in Rabbits. Rabbits are widely used for antibody production, but the immunization techniques, primarily those that involve the use of Freund's or acrylamide adjuvants, provoke considerable inflammation and pain. Investigators at the University of Missouri's diagnostic and investigative laboratory have evaluated a subcutaneously implanted chamber for polyclonal antibody production. The chamber, a sterilized soft plastic golf ball, was implanted and antigen injected into it through one of the perforations in the chamber wall. Fluid volumes of 12 to 22 milliliters could be removed from the chambers at weekly intervals, and the antibodies produced were equal to or better than serum antibodies produced by adjuvant injection. Comfort of the rabbit, ease in chamber immunization, and recovery of high titered antibody in large volumes make this an attractive and humane method for polyclonal antibody production.

Brain-Specific Strains of HIV. Some variants of HIV may have adapted to be preferentially expressed in brain tissue. Scientists at Johns Hopkins University School of Medicine in Baltimore, Maryland, isolated HIV from the brain and cerebrospinal fluid of a patient who had AIDS dementia complex (ADC), a progressive deterioration of the brain that strikes about one-third of all AIDS patients. The researchers inserted bits of the viral genome and a marker gene into fertilized mouse eggs to create transgenic animals. The marker protein was detected in the neural tissue of the mice, which indicates that neurons can supply the cellular machinery necessary for HIV-directed protein production. This mouse model will help researchers better understand how HIV affects the central nervous system of patients with ADC.

Dr. David S. Woodruff of the University of California, San Diego, and his colleagues have developed a new method for genotyping nonhuman primates. This noninvasive technique, which involves analyzing DNA extracted from hair samples, promises to be more efficient and precise and less expensive than existing methods of genetic analysis.

Courtesy of Dr. David S. Woodruff

AIDS Animal Models Program

Hair Samples Provide Clues to Genetic Heritage. Using an elegant technique developed at the University of California, San Diego, scientists can extract and amplify genetic material from a single strand of hair from a nonhuman primate, and thus determine its genetic lineage. Understanding pedigree relationships helps to prevent inbreeding and ensure the genetic variability of an animal colony. The new technique, based on the polymerase chain reaction, is far more efficient and precise and less expensive than analyzing blood or tissue samples with existing methods. In a matter of hours investigators can generate nearly a million copies of DNA fragments that have been extracted from hair samples. Because the hair samples need not be fresh, this method can also be adapted for use in field studies to determine the heritage of free-ranging monkeys, gibbons, or chimpanzees.

Biomedical Research Support Program

Program Description

The Biomedical Research Support Program (BRSP) encompasses several grant programs that enhance biomedical research at supported institutions by meeting critical research and human resource needs. These programs promote innovation, bolster research infrastructure, and strengthen science education. In FY 1992 appropriations for these grant programs totaled $22.8 million.

In addition to the long-established Biomedical Research Support Grant (BRSG) and Shared Instrumentation Grant programs, the BRSP also includes three science education programs targeted to precollege students and teachers. The oldest of these programs, the Minority High School Student Research Apprentice (MHSSRA) Program, has provided hands-on laboratory experience to minority high school students for more than a decade. In FY 1992 the MHSSRA Program was expanded to include teachers in elementary schools, middle schools, and junior high schools. High school teachers have participated in the program since FY 1991. A second education program, the Science Education Partnership Award (SEPA), is a joint initiative of NIH and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Now in its second year, SEPA fosters partnerships among educators, biomedical researchers, and local communities with the goal of increasing science literacy. If successful, these innovative pilot programs will be replicated across the country to promote an understanding of science among precollege students and the general public. The Science Teaching Enhancement Award Program, a pilot program established in FY 1992, strives to help precollege science teachers take a leading role in improving the quality of science education.

Biomedical Research Support Grant Program

The BRSG Program complements and enhances other NIH grant support for biomedical and behavioral investigations. In FY 1992 the objectives of the BRSG Program were narrowed to focus on one major category of needs that the program had previously attempted to meet: support for critical needs of biomedical research projects that were unmet by other funding mechanisms such as the traditional project-oriented, investigator-initiated research project grants. Allowable use of BRSG funds was limited to these categories:

- **Pilot research.** Small short-term projects that explore new research ideas (including multidisciplinary collaborations to explore new directions in biomedical research), test their validity, and seek preliminary findings that may provide the basis for research project grant applications.
- **New investigators.** Initial research support for new investigators and for newly relocated investigators in the process of applying for longer-term funding.
- **Unexpected requirements and opportunities for projects supported by other NIH funding mechanisms.** This includes funding to help research programs continue during temporary lapses in project grant support.

These uses exploit the capacity of the BRSG Program to respond promptly to short-term, low-cost needs essential to enhance the effectiveness of research project grants.

The FY 1992 appropriation included $5.2 million for the BRSG Program, a 77-percent reduction from the FY 1991 appropriation of $22.2 million. A minimum of 628 institutions would have been eligible for the formula-based support. However, with an appropriation of $5.2 million, the amount of funds dispersed on a formula basis to the 628 institutions would have been too small to ensure maximum utility of the funds. Therefore, the FY 1992 BRSG Program was reformatted to concentrate the impact of the awards. A total of 104 1-year awards were made as competitive grants of $50,000 each (no indirect costs were included) following an NIH-based administrative review of applications and second-level review by the National Advisory Research Resources Council. Awards were distributed evenly among the top, middle, and lower third of the institutions ranked on the basis of NIH research grants in FY 1991. Medical schools and graduate schools each received 28 percent of the awards, hospitals 11 percent, research organizations 9 percent, and other health professional schools the remaining 24 percent of the awards.

Shared Instrumentation Grant Program

Expensive high-technology instrumentation is a prerequisite for cutting-edge health research. Today's commercially available instrumentation has reached new heights of sensitivity, flexibility, and computational power, providing unparalleled opportunities to resolve fundamental problems on the cause and cure of various diseases, including hypertension, cancer, AIDS and other infectious diseases, vascular disease, and drug addiction.

Examples of these new instruments include powerful new NMR imagers, coupled hybrid mass spectrometers, and the latest in gene sequencing equipment. Combined with improved computational and graphics software, these technologies have opened up new horizons in biological structure analysis, allowed questions to be asked that could not be posed before, and enabled researchers to move in new scientific directions. Additionally, researchers are faced with the rapid emergence of entirely new instruments. For example, scanning confocal microscopes, not commercially available until recently, have revolutionized the field of cell biology by introducing the capability of dynamic three-dimensional microscopy of living cells. Unfortunately, these new state-of-the-art instruments are very expensive (more than $100,000) and cannot be obtained on an individual research grant. In times of limited resources, the costs of this instrumentation and the fact that the effective lifetime of an advanced instrument is getting shorter and shorter make sharing a driving imperative. The Shared Instrumentation Grant (SIG) Program offers a cost-effective solution to these problems since groups of NIH grantees (an average of eight users) can compete for an instrument in the $100,000 to $400,000 cost range. Between FY 1989 and FY 1992 the SIG Program received more than 400 applications per year, requesting a total of more than $115 million annually. This application rate reflects the increasing need of a broad cross-section of basic and clinical NIH-funded investigators for sophisticated instrumentation, not only to enhance the goals of their ongoing research programs but also to take advantage of these new technological advances to open up new scientific areas.

In FY 1992 the SIG program suffered a severe reduction in funding from $32.5 million to $8.7 million. The program received 400 applications requesting a total of $95.1 million. Of these, 39 applications were funded. The average SIG award was approximately $230,000, about the size of a research project grant. More than 400 NIH-funded grantees were major users of these instruments. Had these users been awarded this equipment individually, it would have cost eight times more, showing the cost effectiveness of this program.

Some examples of NIH-funded research projects that require the unique capabilities of the instruments provided through the SIG Program are summarized under "Research Highlights."

Science Education Programs

Minority High School Student Research Apprentice Program. Relative to their representation in the general population, minority Americans are severely underrepresented in scientific and health fields at every level, from the professional work force—physicians, dentists, and scientists—through all levels of the educational system. The MHSSRA Program targets minority participation in research at the precollege level, a key point in the educational process. The program is designed to fan high school students' interest in biomedical careers by pairing them with a mentor in an active research laboratory for 6 or 8 weeks. The students are given their own independent research projects to carry out, which exposes them to the latest concepts in cellular or molecular biology, human genetics, neuroscience, and the behavioral aspects of diseases. Interaction with the investigators in a stimulating environment stirs the students' curiosity and prompts the understanding of scientific concepts far beyond that achievable through a textbook. Since its inception in FY 1980 the MHSSRA Program has reached a broad cross-section of minority students including African Americans, Hispanics, Asians, Native Americans, and other ethnic groups.

A newly implemented facet of the program provides an indepth laboratory experience for high school science teachers, an opportunity that can translate into more lively enthusiasm for teaching science in the classroom. In FY 1992 the program was expanded to include elementary, middle, and junior high school teachers as well as senior high school teachers. The connections established between researchers and educators foster continued mentoring and encourage young students K-12 to become interested in seeking careers in bioscience.

Funding for the MHSSRA Program was increased from $8.3 million in FY 1991 to $8.9 million in FY 1992. The program benefited more than 3,000 students and 570 science teachers at 385 institutions across the country in FY 1992. The MHSSRA Program teacher positions increased approximately 20 percent over FY 1991. Each position was funded at

Dr. Danny H. Kohl, professor of biology at Washington University in St. Louis, Missouri, shows a class of junior high school students that a feather and a piece of lead fall equally fast in a vacuum. Dr. Kohl participates in the science outreach program funded by a Science Education Partnership Award to Washington University by the Biomedical Research Support Program, NCRR.

Washington University

$5,000, which included supplies and other research needs.

Science Education Partnership Award (SEPA) Program. The NIH SEPA Program, launched in FY 1991, funded 12 pilot programs aimed at increasing the science literacy of both students in grades K-12 and the general public. The model programs, which are funded for up to 3 years, run the gamut of science education possibilities. All are examples of how scientists, educators, media experts, and community leaders can work together to foster excitement about the health sciences in young people and the public.

The first annual SEPA meeting, held in Washington, DC, in April, also included representatives of the 12 SEPA programs funded by ADAMHA. During the day-and-a-half meeting, the program directors reviewed the progress of their programs and discussed networking to increase cross-fertilization among the programs. Evaluation of the 24 diverse programs was a prime consideration. Eventually the successful ones will be widely replicated in other communities. The program has been greeted with enthusiasm by educators at all levels and received excellent media attention in the local communities.

Science Teaching Enhancement Award Program. The start of the Science Teaching Enhancement Award Program (STEAP) in FY 1992 began a new program initiative to further implement the PHS/NIH Life Science Education Goals, the NIH Strategic Plan, and the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET) objectives. The purpose of the 2-year pilot program is to test the feasibility of preparing science teachers (grades 6-12) to become lead or master teachers. These teachers would be trained to take leadership roles in acting as liaisons between biomedical research scientists and their host institutions and science educators, school administrators, and others in their local school systems to improve the quality of precollege science education. Since STEAP is a pilot program, initial eligibility was limited to states that would broaden the geographic areas served by NIH and open the scientific pipeline to a wider range of future biomedical scientists. Twenty applications were reviewed; five awards were funded. These awards will fund the training of a minimum of 15 lead teachers in South Carolina, Kentucky, Maine, Nebraska, and Nevada.

Research Highlights

Biomedical Research Support Grants

Exercise Reduces Breast Milk Palatability. Infants seem to prefer the taste of breast milk before their mothers have exercised, whereas milk collected after 10 or 30 minutes of exertion causes many babies to fuss or cry, according to BRSG-funded researchers at Indiana University in Bloomington. Post-exercise breast milk was found to contain higher levels of lactic acid, a sour-tasting compound that builds up in muscles during strenuous physical activity.

The 26 lactating women who participated in this study collected samples of breast milk before exercising and after briskly walking on a treadmill. Mothers then fed small amounts of each sample to their babies and rated the infants' acceptance of the milk. The women did not know whether the samples contained pre- or post-exercise milk.

Infants preferred pre-exercise milk by a significant margin. The scientists suggest that mothers should consider nursing or collecting milk for later feedings before exercising, since lactic acid levels remain elevated in breast milk for at least 90 minutes after exertion.

Genetic Marker for Prostate and Bladder Cancer. Prostate cancer, the most prevalent form of cancer in American men, is the second leading cause of cancer-related deaths. Understanding the biochemical and genetic changes that occur with this disease could lead to earlier diagnosis and treatment.

Using a Biomedical Research Support Grant of $10,000 as seed money, a new investigator at the University of Texas M. D. Anderson Cancer Center in Houston was able to set up her laboratory while waiting for longer term support. With the additional funding she eventually received, this researcher and her colleagues elucidated some of the biochemical alterations that occur with human prostate and bladder cancer.

Focusing on a cancer-associated gene known as c-*erb* B-2/*neu*, the BRSG-funded scientist and her colleagues were the first to discover that the protein product of this gene is associated with bladder cancer, the fifth most prevalent cancer among adults in the United States. More recently the investigators demonstrated that the c-*erb* B-2/*neu* protein is also present in prostate tumors, and its concentration may be influenced by steroid hormones. The scientists suggest that the c-*erb* B-2/*neu* protein may serve as a diagnostic marker for bladder and prostate cancer progression, allowing physicians to identify these diseases at an earlier stage and to evaluate the success of treatment.

Genetically Engineered Virus Kills Tumor Cells. A team of researchers in Boston, Massachusetts, has produced a genetically engineered virus designed to destroy the rapidly dividing cells of brain tumors while leaving most normal brain cells unharmed. Bolstered by BRSG support totaling more than $24,000 over 3 years, a scientist at Harvard Medical School and his collaborators are developing novel approaches for the treatment of gliomas, the most common type of malignant brain tumor.

At the heart of their potential therapy is a genetically engineered mutant of the herpes simplex virus. This mutant has a limited ability to thrive in nondividing cells. Because tumor cells divide rapidly but normal brain cells do not, the researchers speculated that the mutant herpesvirus would multiply in, and ultimately destroy, glioma cells.

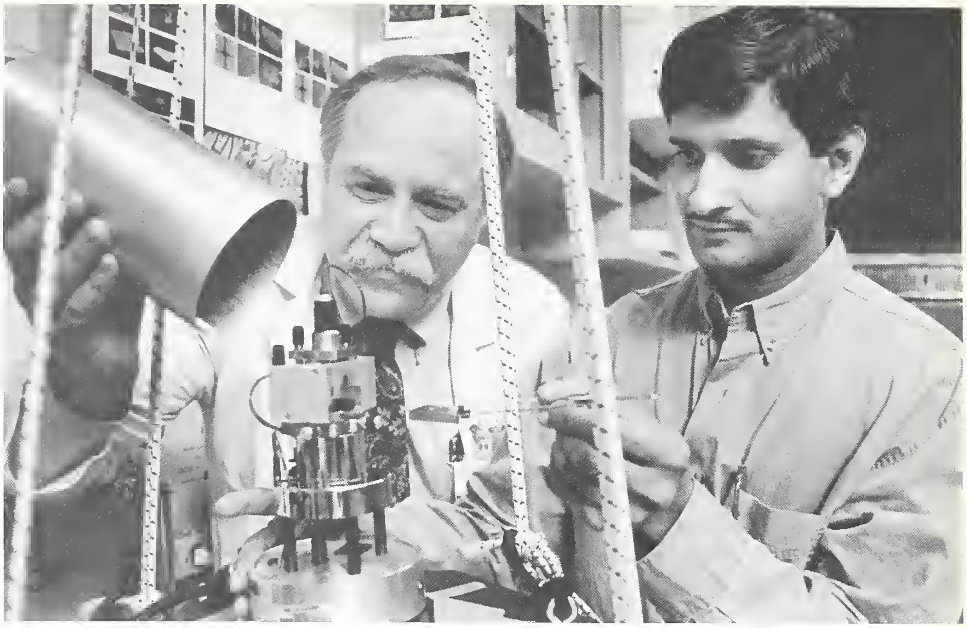
Further studies confirmed that the genetically engineered virus kills human glioma cells in vitro and in mouse models of the disease. Some surviving mice, however, showed evidence of damage from viral infection. The scientists are now testing other viral mutants that may be less harmful to normal tissue but equally lethal to tumor cells.

Dissecting Cellular Gap Junctions. To uncover the fine details of cellular structure, BRSG-funded scientists at the California Institute of Technology (Caltech) in Pasadena have trained their microscopes on the membrane constituents known as cellular gap junctions. Gap junctions are tiny cell-surface pores that allow small molecules and electrical signals to pass from one cell to another. These intercellular connectors are believed to play an important role in many physiological processes, including coordination of muscle contractions, growth regulation, and maintenance of normal body metabolism.

By sheer chance the BRSG-funded scientists discovered that an atomic force microscope

With BRSG support, Dr. Robert L. Martuza and his associates at Harvard Medical School and Massachusetts General Hospital in Boston have developed a mutant herpes simplex virus. The genetically engineered virus is designed to kill human brain tumor cells but leave surrounding tissue unharmed.

Joshua Touster



Drs. Morton Arnsdorf (left) and Ratneshwar Lai, of the University of Chicago in Illinois, inspect an atomic force microscope (AFM), which is suspended from elastic cords to protect it from vibrations. The scientists and their BRSG-funded colleagues at the California Institute of Technology in Pasadena used AFM to dissect and visualize cellular gap junctions in a natural, watery environment.

Randy Tunnell, University of Chicago

(AFM), which can provide atomic-level resolution of surfaces, could also be used as a tool for dissecting cellular structures. AFM involves scanning a sensor that is only a few atoms thick at the tip across a specimen and recording deflections as the tip moves. The Caltech investigators used the instrument's sharp tip to peel away the thin upper membrane from isolated gap junctions.

With the underlying membrane thus exposed, the scientists could discern several closely packed structures, presumably the channel openings of gap junctions. These images are compatible with other visualizations of gap junctions obtained by electron microscopy and x-ray diffraction.

Now working to improve the resolution of their images, the scientists say AFM may one day be applied to dissecting and scrutinizing the details of other cellular components. Because AFM allows viewing the specimens in a watery environment, this technology also may be used to see how drugs attach to cellular receptors or how antibodies and membrane proteins interact.

Shared Instrumentation Grants

Three-Dimensional Structure of AIDS Virus Enzyme. With the aid of an x-ray area detector system and a DNA synthesizer purchased with SIG support, scientists at Yale University in New Haven, Connecticut, have uncovered the three-dimensional structure of reverse transcriptase, an enzyme that plays a key role in AIDS virus infections. With detailed knowledge of the enzyme's form, scientists can more easily identify drugs that bind to and block the action of reverse transcriptase, possibly halting viral replication.

To determine the enzyme's shape, the researchers grew crystals of reverse transcriptase coupled to the enzyme inhibitor nevirapine, a potential anti-AIDS drug. The crystals were then irradiated with X rays, and the intensities of diffracted rays were measured using the detector system that had been purchased with SIG funds. The x-ray diffraction data were processed through a computer to produce three-dimensional images of the enzyme-inhibitor complex.

Current anti-AIDS drugs like AZT hinder the action of reverse transcriptase, but the gene that encodes the enzyme often mutates and eventually becomes resistant to these drugs. Now that the detailed three-dimensional structure of reverse transcriptase is known, scientists hope to avoid the problem of drug resistance by identifying compounds that more specifically bind to active sites on the enzyme.

Powerful NMR Magnet Improves Study of Alzheimer's Disease, Stroke. Researchers at Henry Ford Hospital in Detroit, Michigan, are elucidating the biological mechanisms that underlie Alzheimer's disease, stroke, and other brain disorders, thanks to a powerful nuclear magnetic resonance (NMR) magnet purchased with $400,000 in SIG support. This 3-tesla superconducting magnet, with a magnetic field 60,000 times stronger than that of the earth, is the world's largest hospital-based magnet dedicated to the study of the human brain. By comparison, most hospital-based magnets used for diagnostic purposes are in the 0.5- to 2-tesla range.

Noninvasive studies with the magnet have already uncovered a direct link between high acidity in the brain and adverse effects of stroke. Scientists now hope to determine whether controlling the acidity of a stroke victim's brain will minimize the chances of incurring lasting disability such as paralysis.

In studies of Alzheimer's disease now under way, the investigators are examining phosphorus metabolism in the brain, hoping to find a diagnostic marker that will differentiate Alzheimer's disease from other types of dementia. This research was recently buoyed with additional funding from the National Institute on Aging.

Glaucoma Rates Tracked Among African Americans. In a study of more than 5,000 residents of a racially mixed neighborhood in Baltimore, Maryland, scientists found that African Americans have a significantly higher risk of developing primary open-angle glaucoma (POAG) than do Caucasians. These findings suggest that blacks have an underlying genetic susceptibility to POAG, an eye disease that damages the optic nerve and ultimately leads to blindness if left untreated.

To analyze the extensive data collected in this population-based epidemiological survey, the researchers employed sophisticated data-processing and computing equipment purchased with SIG funding. The analysis showed that the risk of developing POAG was four to five times greater among blacks than among whites. This divergence is first detectable in middle age, and the differential rises with increasing years. Among those aged 70 and over, nearly 1 of every 10 African Americans but only 1 of 40 Caucasians had POAG.

Based on these findings, the researchers suggest that public health efforts focus on identifying and preventing POAG-related blindness among African Americans. Further analyses of family pedigrees are needed to pave the way for genetic mapping, which may ultimately help to pinpoint the gene or genes responsible for POAG.

As part of a large epidemiological survey, Dr. Alfred Sommer inspects a Baltimore, Maryland, woman for signs of primary open-angle glaucoma, an eye disease that can cause blindness. Computing equipment purchased with SIG funding allowed researchers at Johns Hopkins University School of Medicine to analyze the massive amount of data collected during the 4-year survey.

Photo courtesy of Johns Hopkins University

NMR Studies Elucidate Brain Structure and Function. With the assistance of several SIG awards totaling more than $1 million, the NMR Center of Massachusetts General Hospital (MGH) in Boston has acquired state-of-the-art imaging equipment that is now reaping big payoffs in studies of the human brain. Using a 1.5-tesla real-time NMR imaging system, the BRSP-supported researchers are developing novel strategies for noninvasive measurement of cerebral blood volume. These techniques are being used to assess the aggressiveness of brain tumors in patients and to learn more about brain activity during cognitive processes.

In addition to the various imaging techniques that have long been used to map cerebral blood flow, assessment of blood volume can provide insights into the workings of the brain. The MGH scientists used a new magnetic resonance imaging (MRI) technique known as echo planar imaging to produce high-resolution in vivo maps of blood volume, which seemed to correlate with the severity of patients' brain tumors. Maps of this type may one day be used to guide physicians during tumor biopsy and to evaluate the effectiveness of tumor treatments.

In related studies the investigators produced the first MRI maps that revealed changes in brain physiology resulting from human mental processes. Volunteers wore special goggles that flashed bright lights. During light stimulation MRI maps showed that blood volume increased significantly within the primary visual cortex. It is hoped that research in this area will elucidate the structure-function relationships involved in information processing in the brain.

Minority High School Student Research Apprentice Program

MHSSRA Student Winners in 1992 Westinghouse Science Talent Search. Three 17-year-old MHSSRA students were among the 40 finalists in the 1992 Westinghouse Science Talent Search, a prestigious national contest sponsored jointly by Westinghouse Electric Corporation and Science Service, Inc.

One of the winning high school students was honored for her molecular biology studies of lung cancer tumors. This student, from Monterey Park, California, cloned the human gene for the enzyme aldehyde reductase and evaluated the levels of messenger RNA that codes for this enzyme in tumor cells. Her ultimate goal is to determine how aldehyde reductase may contribute to the dangerous side effects of a cancer drug known as daunorubicin. She plans to study biochemistry and pursue a career as a physician or medical researcher. Another student, who plans to study biology and become a surgeon, was recognized for his studies of an enzyme found in the membrane of yeast cells. This student, from Staten Island, New York, identified molecular regions that are important for proper enzyme activity.

A third student winner studied a human enzyme that helps to control blood pressure. This high school student, from Holliswood, New York, analyzed the kinetics of enzyme inhibition, crystallized the enzyme bound to an inhibitor, and performed computer modeling of the enzyme's mechanism of action. During his MHSSRA-funded apprenticeship at the Medical Foundation of Buffalo, New York, the student benefited from earlier BRSP awards to that institution. BRSG funding bolstered crystallography and structural biology research at the Medical Foundation of Buffalo, and funds from the SIG Program provided some of the advanced instrumentation used by the student in his studies.

Alabama Teachers, Students Benefit From "Bioteach" Program. As part of the BRSP initiative to bring more excitement and learning experiences to precollege science classrooms, professors at the University of Alabama at Birmingham (UAB) offer a 6-week summer science course to middle- and high-school teachers across the state. Known as "Bioteach," this intensive program combines lectures, laboratory work, and field trips to enhance the teachers' understanding of basic science and new technologies. The program is funded with the combined support of the MHSSRA Program, UAB, and local companies.

Topics under study range from bacterial genetics to recombinant DNA technology to the molecular biology of cancer. The 25 teachers who attended Bioteach in 1992 are now expected to bring these learning experiences back to their own classrooms, offering their students a better understanding of how science influences everyday life. In this way Bioteach benefits hundreds of students across the state of Alabama.

High school science teachers Mary Ann Williams, Mary Anchors, and Patrick Crowder study the results of a DNA sequencing project they conducted as part of the MHSSRA-funded "Bioteach" program at the University of Alabama at Birmingham. Teachers who attend this summer laboratory-based course bring a greater enthusiasm and a broader understanding of science back to their classrooms in the fall.

Hal Yeager, *The Birmingham News*

Jeremy P. Bent, a 12th grade participant in the Minority High School Student Research Apprentice Program, gained hands-on laboratory experience during his summer apprenticeship at Howard University College of Medicine in Washington, DC.

Jeffrey John Fearing, Howard University College of Medicine

High School Science Day at NIH. Sixty high school students and teachers from the Washington, DC, area attended the MHSSRA-sponsored 1992 High School Science Day on the campus of NIH in Bethesda, Maryland. Students and teachers who had summer apprenticeships at the University of the District of Columbia, George Washington University, Georgetown University, or Howard University participated in the all-day session, which included presentations by minority scientists and tours of the National Library of Medicine and the NIH Clinical Center. The meeting was designed to further enrich the summer science experience of participants in the MHSSRA Program.

Science Education Partnership Awards

Nutrition and Health Studies Enhance Middle-School Science. In a unique partnership, NIH-funded researchers and middle-school science teachers in Ohio are developing science curricula that emphasize simple, hands-on laboratory experiments to teach students in grades 5-8 about nutrition and human growth. Once tested and finalized, these lesson plans may be made available to other middle-school teachers across the country.

A medical researcher at Ohio State University (OSU) in Columbus is overseeing this 2-year $200,000 SEPA project, which complements his larger ongoing study of how dietary calcium and genetic factors influence bone mass formation among adolescent girls. More than 400 girls are participating in this larger 4-year investigation funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

In collaboration with biomedical researchers at OSU, 13 middle-school teachers from 6 school districts developed lesson plans and innovative laboratory projects in which students study themselves and their families to learn more about health and nutrition. Laboratory exercises will also replicate or draw on data collected in the ongoing NIAMS study. In each classroom activity students are required to generate a hypothesis or make predictions that can be tested.

By taking body measurements, analyzing physical measurements of family members, and maintaining physical activity and food intake logs, students are expected to gain a more sophisticated understanding of science and to appreciate the personal relevance of biomedical research. In this educational project, like all SEPA partnerships, scientists, educators, and the community combine forces to increase scientific literacy and interest in the health sciences among young people and the public.

Biological Models and Materials Research Program

Program Description

The Biological Models and Materials Research Program (BMMRP) supports and promotes increased development and use of nonmammalian model systems in biomedical research. Such model systems may help conserve the limited supply of mammalian animal resources and allow studies that are not feasible in higher organisms.

A major effort of the BMMRP is to expand the variety and utility of models that provide information useful for understanding human physiology and diseases. Model systems supported by BMMRP include invertebrates, lower vertebrates (limited to poikilothermic, or cold-blooded, organisms), microorganisms, cultured cells, and nonbiological systems such as computer simulations and mathematical models. In FY 1992 the BMMRP funded 53 research projects and resource facilities with its $8.4 million appropriation. Among the 44 research projects are various high-connectivity models, which are organisms or biological systems about which a large body of knowledge is available. The organisms are connected or crosslinked by the characteristics and properties shared with other taxa.

Among the organisms that are considered high-connectivity nonmammalian models is the small roundworm *Caenorhabditis elegans,* which has been adopted as a model organism for a variety of biomedical research applications, especially in the area of genetics. Through its continued funding of the Caenorhabditis Genetics Center and research project grants, BMMRP has supported the development of the *C. elegans* model. The zebrafish is another BMMRP-supported organism that has great potential as a high-connectivity model. This 2-inch freshwater fish will be invaluable for the development of transgenic techniques in fish. Although zebrafish were first considered as a model organism more than 20 years ago, they are just now beginning to be accepted. Other high-connectivity systems include a model for epithelial basement membrane interactions using hydra, a freshwater organism; a supercomputer simulation of the mammalian kidney; development of transgenic fish for biomedical research; and hormonal regulation in *Drosophila*.

The BMMRP supports a number of resource centers, including facilities that supply materials critical to progress in biomedical research. These resources assist individual scientists by providing biomaterials and organisms, maintaining normal and abnormal cells of many species, establishing methods for laboratory culture of nonmammalian marine organisms, and developing collections of valuable biomaterials such as cloned genes, DNA probes, and human chromosome libraries. Such centers include the American Type Culture Collection (ATCC) in Rockville, Maryland; the National Disease Research Interchange in Philadelphia, Pennsylvania; the Caenorhabditis Genetics Center (CGC) in St. Paul, Minnesota; the Center for Alternatives to Animal Testing at Johns Hopkins University in Baltimore, Maryland; the Laboratory Culture of *Hermissenda* at the Marine Biological Laboratory in Woods Hole, Massachusetts; the Marine Biomedical Institute in Galveston, Texas; the Yeast Genetic Stock Center at the University of California, Berkeley; the Repository of Mice and Human DNA Probes and Human Libraries located at the ATCC; and the National Cell Culture Center in Minneapolis, Minnesota.

The BMMRP also supports projects to develop new biomaterials and provides core support for established centers that make nonmammalian model systems more accessible for research. For example, the program supports an effort at the University of British Columbia in Vancouver, Canada, to provide researchers who study *C. elegans* with a comprehensive genetic resource, in particular a genetic toolkit of chromosomal balancers. Chromosomal balancers are rearrangements that suppress genetic recombination. Genetic stocks of *C. elegans,* which are supplied by CGC, are expected to help in isolating and mapping mutations in any part of the *C. elegans* genome. This project has been under way for approximately 1 year and has already produced balancers for several chromosomes.

Small Grants Program. In 1992 BMMRP received its first grant applications for a new Small Grants Program to fund high-risk, innovative research to develop nonmammalian models that have the potential for becoming useful biomedical tools. A good response was received with a wide diversity of applications and 14 proposals were funded, includ-

Zebrafish are an ideal model for developmental and transgenic studies of vertebrates because their transparent eggs allow detailed study of embryo development. At the University of Minnesota BMMRP-supported scientists study transgenic zebrafish to determine how expression of the thyroid hormone receptor gene affects normal development.

Courtesy of Dr. Perry Hackett, University of Minnesota ing the development of an insect model for the assessment of pro-oxidant toxicity, a *Drosophila* model to study insulin-dependent signals, a heart model using a marine tunicate, squid skin as a model to study calcium antagonists, a marine chordate model for kidney stone disease, a lobster model for muscle development, studies of circadian rhythm using a lizard, and a paramecium to study thermoregulation at the cellular level.

Biomatrix. During 1992 the BMMRP continued its support of projects related to the matrix of biological knowledge (Biomatrix). The Biomatrix is defined as the organization, or complete databases, of all published biological and clinical data, and the theories and analyses of these data. To accomplish this, a mechanism to organize and intelligently access the large array of biological information needs to be developed. Researchers at SRI in Palo Alto, California, in collaboration with investigators at the Marine Biological Laboratory in Woods Hole, Massachusetts, have begun a BMMRP-funded project to collect data on the genes and metabolism of the bacterium *Escherichia coli* and to encode this information in a computer database. The resulting program will allow investigators to access genetic and metabolic data in a graphic, user-friendly manner.

Program Highlights

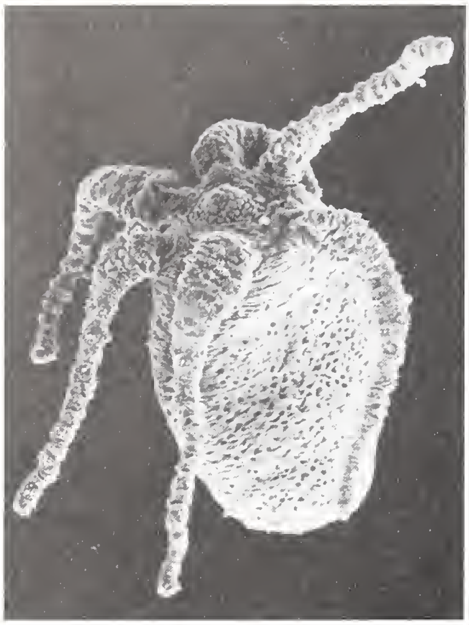
Caenorhabditis Genetics Center. In mid 1992 the BMMRP-supported Caenorhabditis Genetics Center (CGC) moved to a new location at the University of Minnesota in Minneapolis. The entire collection of over 1,600 strains of the *C. elegans* and related nematode species was transferred to the new center. This small roundworm, only a millimeter long, has become one of the premier model organisms for developmental geneticists because the complete cell lineage of the organism is known. Every cell division, from the single-cell zygote to the adult worm, has been traced. More than 1,200 mutant strains were distributed by the CGC to researchers in the past year.

New* C. elegans *Gene Discovered. The study of model organisms may provide insights into the nature of human diseases and disorders. Researchers at the Massachusetts Institute of Technology in Cambridge have discovered a new *C. elegans* gene named ced-9, which prevents cells from undergoing programmed cell death by regulating the activities of other genes. The ced-9 gene has many similarities to the human oncogene bcl-2, which also may regulate active cell death processes. Thus protection from programmed cell death might be an important phenomenon found in invertebrates and vertebrates and may give researchers clues to understanding human disorders such as neurodegenerative diseases and stroke that are characterized by extensive cell death.

Marine Biotechnology. The BMMRP cosponsored the International Marine Biotechnology Conference held in Baltimore, Maryland. This conference brought together over 400 researchers from around the world to discuss topics as diverse as novel marine-based industrial materials and energy; the use of bioactive marine products, such as toxins and venoms, as pharmaceuticals; bioremediation of marine oil spills using microscopic marine organisms; and harvesting the marine environment for food. A large part of the meeting was devoted to the development of transgenic fish species, which have become important

The Caenorhabditis Genetics Center serves as a clearinghouse for the development, maintenance, and distribution of mutants of C. elegans, *a tiny roundworm that serves as a model for mapping the human genome. Dr. Robert K. Herman is the new director of the center, which recently moved from Columbia, Missouri, to the University of Minnesota in Minneapolis.*

Tom Foley, University of Minnesota



Hydra vulgaris, *the freshwater organism shown in this scanning electron micrograph, is being developed as a nonmammalian model for the study of diabetes mellitus. BMMRP-funded scientists at the University of Kansas Medical Center in Lawrence are studying how a membrane in the hydra's body changes in response to glucose. This research may shed light on pathological changes that occur in the tissues and certain membranes of diabetic patients.*

Courtesy of Dr. Michael P. Sarras Jr., University of Kansas Medical Center

models in a number of scientific areas, including vertebrate development, neurobiology, and endocrinology.

BMMRP supported studies of vertebrate development that utilize fish white blood cells. Researchers at Oregon State University in Corvallis have been working on ways to improve the results obtained in in vitro assays on these cells. They found, for instance, that cells that were previously unresponsive to stimulating agents could be made to respond by culturing them in the presence of fish serum rather than fetal bovine serum, the standard culture medium supplement. This discovery will allow researchers to expand the number and types of experiments that can be done with these cells.

Disease Models and Potential Treatment. Progress in the war against disease depends not only on a steady flow of insights from researchers employing models but also on research based on both a variety and a combination of models. BMMRP is committed to encouraging such variety and supports both investigator-initiated research using nonmammalian models and resources that provide materials to researchers studying aspects of disease. For example, BMMRP last year supported research on diabetes mellitus in two separate, distinct ways.

Researchers at the University of Kansas Medical Center in Lawrence used *Hydra vulgaris* to develop a model for the thickening of the basement membrane in kidney tubules and blood vessels that may occur in individuals with diabetes mellitus. Hydra are small freshwater invertebrates that live in colonies and spend their adult lives attached to a rock. This morphologically simple animal is composed primarily of two layers of epithelial cells with a basement membrane sandwiched between them; thus it is ideally suited for studies of basement membrane changes. The basement membrane is a critical support for the epithelial cells that line the kidneys and blood vessels, and thickening can result in complications of diabetes such as retinopathy, neuropathy, accelerated atherosclerosis, and nephropathy. Using this model, researchers have shown that increased levels of glucose similar to those seen in diabetic patients induce a thickening of the hydra basement membrane within 3 to 4 days. Future studies will attempt to learn how glucose produces this effect and search for ways to prevent it.

The National Disease Research Interchange contributed to diabetes research by providing large numbers of pancreases to researchers at the Washington University School of Medicine in St. Louis, Missouri, for preparation of the insulin-producing islet cells. Until insulin-dependent diabetes can be prevented, the single most effective treatment is to transplant islet cells from cadaver donors into diabetic patients. Major problems exist, however, in rejection of the donor cells by the recipient. The researchers at Washington University are developing methods to prevent the rejection process and make islet transplantation a practical treatment for diabetes. They found that the presence of white blood cells called lymphocytes, which contaminate islet cell preparations, greatly increases the probability of rejection. These scientists have developed new ways to isolate and store pancreatic islets that may make them less likely to be rejected. A process as simple as storing the donor cells at a low temperature for several days was found to reduce the number of white blood cells in the donor population.

Research Centers in Minority Institutions Program

Program Description

The success of scientific endeavors rests soundly on the intellectual and physical environments in which research is conducted. For the past 8 years NCRR's Research Centers in Minority Institutions (RCMI) Program has worked to enhance the biomedical research environment at minority colleges and universities that award doctoral degrees in the health sciences or sciences related to health by funding improvements to the institutions' infrastructure and by fostering communication and collaboration among investigators.

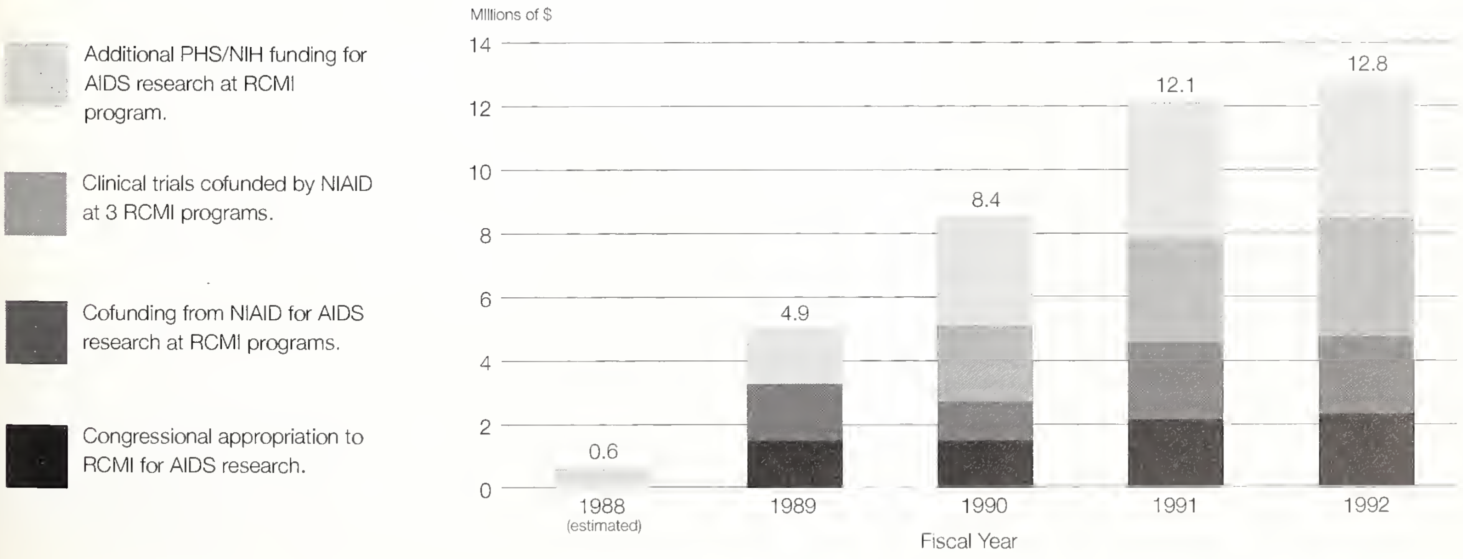
The nation's minority populations—particularly African Americans, Hispanics, Native Americans, and native Hawaiians—are disproportionately affected by a variety of health problems including cardiovascular disease, cancer, diabetes, infant mortality, and AIDS. Recognizing that predominantly minority institutions could play a greater role in improving the health of minority groups—and thereby improve the health of all Americans—Congress in 1985 mandated the establishment of the RCMI Program to bolster the research capacity of these institutions. Since that time the RCMI Program has provided funding to 18 grantees in 11 U.S. states and territories. Strengthened by RCMI support, existing faculty are now able to utilize their expertise to pursue important research questions. Additionally, these institutions are better able to attract other well-trained faculty and garner additional funding from government and private agencies.

RCMI grant awards underwrite the purchase of state-of-the-art instruments and the renovation of laboratories, animal quarters, and other physical facilities. RCMI grants also support pilot projects designed to gather preliminary data that later can be used to compete for independent research support. Recruitment and hiring of new faculty also fall under the aegis of the RCMI Program, as does support for administrative offices in grants management, research development, editorial services, and instrumentation design and maintenance.

The RCMI Program makes awards for up to 5 years on a competitive, peer-reviewed basis to predominantly minority institutions that offer doctorate degrees in the health professions or in a health-related science. In FY 1992 the eligibility requirements were expanded under a new initiative titled "Emerging Doctoral Programs" to also include institutions that are close to having such programs in place.

During FY 1992 grants totaling more than $26 million (including nearly $3 million from the National Institute of Allergy and Infectious Diseases and the National Center for

Funds Awarded to Support AIDS Research at Research Centers in Minority Institutions

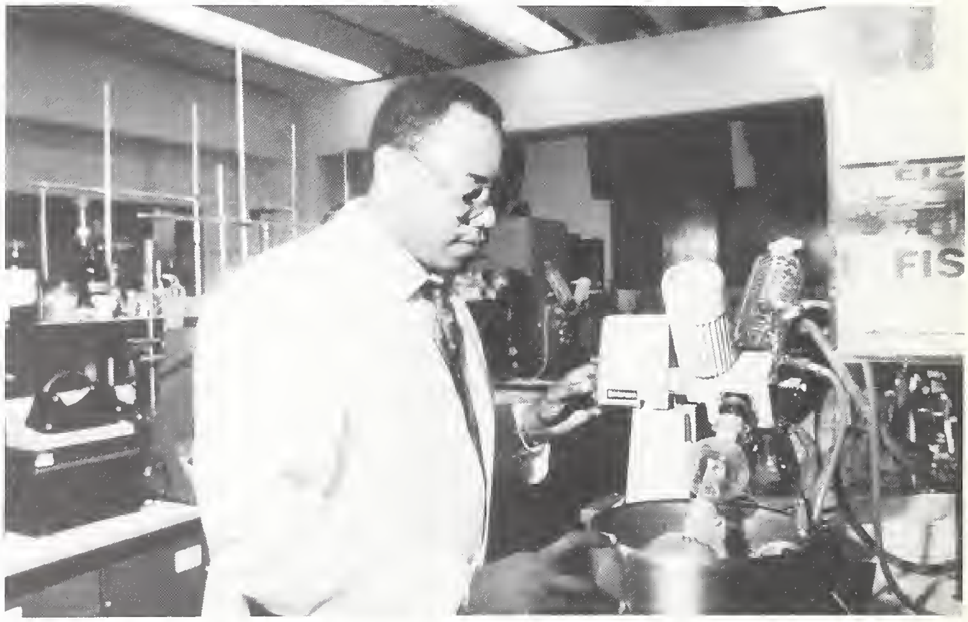


Human Genome Research) were awarded to advance the RCMI Programs at 18 institutions. These RCMI grantees include three colleges of pharmacy, seven medical schools, seven graduate schools, and the only minority school of veterinary medicine in the country.

Among the awards made in FY 1992 were a 3-year renewal grant to the Charles R. Drew University of Medicine and Science in Los Angeles, California, and a 5-year start-up grant to the University of Texas at El Paso. The latter award represents two significant "firsts" for the RCMI Program: It is the first grant to a predominantly Hispanic institution in the Southwestern United States, and it is the first award made under the new Emerging Doctoral Programs initiative. The grant is designed to give an extra boost to the university's proposed Ph.D. program in biomedical sciences and to help establish a biomedical research center to integrate investigations in the areas of cell biology and biostatistics.

Although Emerging Doctoral Programs is a new initiative, the RCMI Program has already fostered the inception of several Ph.D. programs at minority institutions. With the added leverage provided by RCMI support, doctorate programs in the following fields have been launched in the past 6 years: neuroscience at Meharry Medical College in Nashville, Tennessee; biological sciences at Morehouse School of Medicine in Atlanta, Georgia, and at Ponce School of Medicine in Puerto Rico; pharmaceutical sciences at Florida A & M University in Tallahassee; and molecular biology at the University of Hawaii in Honolulu.

The workshops and symposia sponsored by RCMI provide a forum for investigators to share their unique achievements and to pursue common goals. These meetings promote networking and collaboration among research groups and give recognition to the contributions made by minority institutions. The third annual RCMI International AIDS Symposium was held in Atlanta, Georgia, in November 1992. Papers were presented by investigators from many African and Latin American countries disproportionately impacted by the AIDS pandemic, and by RCMI participants and other American scientists. The topics ranged from AIDS surveillance to basic research, vaccine development and clinical trials, and AIDS prevention and education. Hosted by Morehouse School of Medicine, the forum provided a unique and intimate environment for dialogue and development of collaborative interests. At a November 1991 workshop cosponsored by the RCMI Program and the National Institute of Diabetes and Digestive and Kidney Diseases, scientists reviewed recent advances in understanding the epidemiology and genetics of diabetes mellitus in minority populations. The 3-day conference, held in Hawaii, also featured discussions of therapeutic strategies and the pathological effects of the disease. Meharry Medical College hosted a neuroscience symposium and career development workshop in October 1991 to bring together outstanding scientists in the field and provide guidance to graduate students. RCMI also sponsored a May 1992 symposium titled "The World of RNA" at Hunter College of the City University of New York. The meeting explored new findings related to RNA folding and RNA-protein interactions and featured a presentation by Nobel laureate Sidney Altman.



For his studies of anti-inflammatory drugs, Dr. Hugh M. McLean received his Ph.D. in medicinal chemistry from Florida A&M University in Tallahassee. The university's new doctoral program in pharmaceutical sciences was founded in part with the support provided by RCMI.

Florida A&M University

A key objective of the RCMI Program is to identify emerging research opportunities and explore how minority institutions can contribute to the national effort in these areas. With this goal in mind RCMI has entered several collaborative initiatives with other components of NIH. An AIDS initiative begun in FY 1989 with the cooperation of the National Institute of Allergy and Infectious Diseases has continued and expanded in FY 1992. The initiative strengthens support of AIDS-related research at RCMI centers, with the ultimate goal of having these centers participate more fully in all areas of AIDS-related research, including AIDS clinical trials, within the next few years.

A second initiative, a collaboration with the National Center for Human Genome Research (NCHGR), seeks to contribute to international efforts to map the human genome. Clark-Atlanta University in Atlanta, Georgia, and Meharry Medical College both received additional awards in FY 1992 to establish research programs in human genetics, and NCHGR and RCMI are continuing to support human genome studies at Howard University in Washington, DC.

Recognizing that RCMI-eligible dental schools can play a significant role in improving the oral health of minority populations, RCMI and the National Institute of Dental Research launched a new initiative in FY 1992 to develop regional research centers for minority oral health. Three RCMI institutions are participating as the grantee (Meharry Medical College) or as collaborating institutions (Charles R. Drew University of Medicine and Science and Howard University) in 3-year awards granted in FY 1992 to minority dental schools or dental schools that serve large minority populations.

Research Highlights

International Collaborators Study Mammary Gland Function. Recognizing that research is enhanced by cooperative efforts, the RCMI Program strives to enhance opportunities for faculty to interact with key investigators at other institutions. In one fruitful collaboration, RCMI-supported scientists at the University of Hawaii in Honolulu teamed up with researchers at the Hannah Research Institute in Scotland to study how mastectomy, or removal of the mammary glands, can affect pregnancy in the guinea pig. The Scottish scientists earlier had found that mastectomy significantly increased the incidence of stillbirth and newborn deaths in the animals.

Focusing on the hormone relaxin, which induces dilation of the cervix during the birth process, the collaborators found evidence for a unique function of the guinea pig mammary gland. The researchers measured relaxin in uterine tissues from both mastectomized and intact animals before, during, and after pregnancy. Levels of the hormone were considerably lower in mastectomized animals. These findings suggest that the mammary gland, normally considered an exocrine gland for milk production, may also function as an endocrine gland that stimulates relaxin production in the uterus.

Drs. Carolyn Alexander-Caudle and E. L. Myles observe a mammalian cell culture at the RCMI-funded Center of Biobehavioral Research on Health, Tennessee State University, Nashville. These cultures are used to study how nonionizing radiation affects the expression of oncogenes, tumor necrosis factor, and heat shock proteins.

Tennessee State University

Primate Model for Postmenopausal Bone Loss. Scientists at Morehouse School of Medicine in Atlanta, Georgia, have found that an analog of the reproductive hormone gonadotropin-releasing hormone (GnRH) can induce early and reversible menopause in rhesus monkeys. These animals not only serve as a model for human menopause but also can be used to study progression and treatment of postmenopausal bone loss.

In collaboration with investigators at the Yerkes Regional Primate Research Center in Atlanta, RCMI-supported scientists at Morehouse recently discovered that growth hormone administration helps to preserve bone mass in these animals. A group of GnRH analog-treated monkeys lost about 12 percent of their bone mass, whereas animals treated with GnRH analog plus growth hormone showed no significant bone loss. Growth hormone therapy may hold potential for reducing bone loss in menopausal women and in women who take GnRH analogs to treat endometriosis and other conditions. The scientists are now investigating how growth hormone and other compounds help to interrupt the progression of bone loss.

Analysis of HIV Strains From Uganda. RCMI-backed scientists at City College of the City University of New York found evidence that the strains of HIV commonly found in patients in Uganda differ significantly in certain key genetic regions from HIV strains that are prevalent in the United States. These findings could have troubling implications for AIDS vaccine developers, since a vaccine designed for the U.S. population may prove ineffective in other parts of the world.

The investigators isolated the AIDS virus from Ugandan blood samples and cloned segments of the gene that codes for gp120, an HIV surface protein that is a common molecular target for prospective vaccines. The researchers discovered that the gene segments of Ugandan viruses were strikingly different from the corresponding gene segments of American HIV. In light of these findings, vaccine developers might consider targeting

In an RCMI-supported laboratory at Tuskegee University, Tuskegee, Alabama, Drs. Gliceria Pimentel-Smith (left) and Oyewole Adeyemo prepare to test samples for viral proteins.

Tuskegee University

their vaccines to the HIV strains from regions that are disproportionately devastated by AIDS.

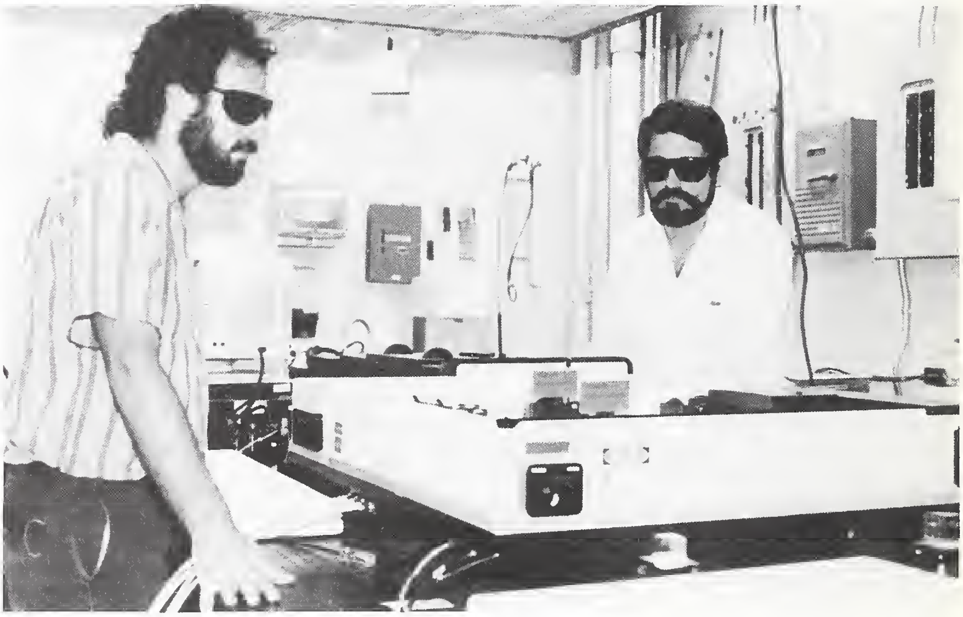
"Leaky" Blood-Brain Barrier in Diabetic Rats. An animal model for diabetes insipidus is also proving valuable in RCMI-funded studies of the blood-brain barrier and the central nervous system (CNS). Researchers at the University of Puerto Rico Medical Sciences Campus in San Juan are investigating the role of the pituitary hormone vasopressin, which is lacking in patients and animals that have diabetes insipidus. Vasopressin contributes to the regulation of blood pressure by a nerve center located in the CNS. The hormone also stimulates blood vessel contraction and regulates urine concentration.

The scientists administered vasopressin to the peripheral circulation of rats with diabetes insipidus. Surprisingly, the hormone apparently crossed the blood-brain barrier and corrected the CNS-mediated regulation of blood pressure, although vasopressin does not cross the blood-brain barrier in normal animals. Later studies confirmed that the hormone was present in the cerebrospinal fluid of vasopressin-treated diabetic rats, which implies that vasopressin was able to enter the CNS from the general circulation.

These findings suggest that the diabetic rat, with an inborn lack of vasopressin, has a "leaky" blood-brain barrier. This hormone may help to maintain the normal properties of the barrier, possibly through effects on blood vessels in the brain known as the choroid plexus.

Nerve Cell Communication. Because of its large nerve cells and simple nervous system, the marine snail *Aplysia californica* has long been employed to uncover the intricacies of communication between neurons. Focusing on the snail's cerebral ganglion, an investigator at Meharry Medical College in Nashville, Tennessee, has characterized two distinct forms of neuron plasticity, or changeability. One form, known as synaptic depression, was seen when a presynaptic—or sending—neuron was stimulated every few minutes and the signal in the receiving neuron became progressively smaller. When the presynaptic neuron was rapidly stimulated for a few seconds, however, the signal in the receiving neuron gradually grew, or potentiated, in a process dubbed slow-developing potentiation.

The RCMI-supported scientist is further investigating how the enzyme protein kinase C may facilitate nerve signal transmission. As ongoing studies of *Aplysia* reveal the basic mechanisms underlying neurotransmitter release and uptake, researchers gain greater insights into the workings of more complex brain systems.



With RCMI support the University of Puerto Rico—Rio Piedras has become one of Puerto Rico's premier institutions for basic science research. Using advanced instruments such as high-field NMR and laser systems, researchers delve into photochemistry, cell and molecular biology, and photobiology. Here Dr. Brad Weiner (left) and Dr. Rafael Arce—wearing protective goggles—conduct studies using an ND:Yg laser.

University of Puerto Rico—Rio Piedras

Intramural Programs

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Library Branch 48
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Veterinary Resources Program 51

Overview of Intramural Research Resources Activities

Program	Funding*	Major Resources
Office of the Director/ Office of Animal Care and Use	$ 4,914,000	
Biomedical Engineering and Instrumentation Program	$ 16,239,000	• In vivo NMR research center • Analytical electron microscopy and ultracentrifugation • Mathematical models • Image processing • Special instrumentation design • Construction, modification, and repair of scientific equipment
Library Branch	$ 4,567,000	• NIH Library • Computerized databases • Translation service • Photocopy service
Medical Arts and Photography Branch	$ 11,744,000	• Computer graphics • Typesetting • Video production • Medical illustration • Photography
Veterinary Resources Program	$ 25,241,000	• Carnivores and ungulates • Nonhuman primates • Rodents and rabbits • Animal genetic resource • Pathology and diagnostic service • Surgery, radiology, and pharmacy service
Total Intramural	$ 62,705,000	

*Funding is provided through the Management Fund (an assessment on all NIH institutes, centers and divisions) and the Service and Supply Fund (a fee-for-service activity). The funding does not include reimbursements or charges related to space costs.

Biomedical Engineering and Instrumentation Program

Program Description

The Biomedical Engineering and Instrumentation Program (BEIP) is a centralized support service for NIH intramural scientists. BEIP physical scientists, engineers, and technical support personnel contribute to biomedical research by providing expertise in the areas of engineering, mathematics, and the physical sciences. Each year BEIP staff members collaborate on more than 200 intramural projects, designing and producing advanced instrumentation, models, and techniques that had been previously unavailable to NIH scientists. BEIP personnel typically respond to an additional 1,500 requests for fabrication or major modification of laboratory equipment, and nearly 10,000 requests for repairs or minor modifications of scientific instruments. The program is divided into two groups: Professional Engineering and Scientific Equipment Services (SES).

Professional Engineering. BEIP's professional engineers and physical scientists do independent research and also collaborate with other NIH scientists on studies involving biomedical measurements, mathematical modeling, imaging, and the design of specialized instrumentation. The professional engineering group comprises four sections: Electrical and Electronic Engineering, Applied Clinical Engineering, Chemical Engineering, and Mechanical Engineering. BEIP also has administrative responsibility for and provides major scientific and technical support to the NIH In Vivo NMR Research Center.

Scientific Equipment Services. BEIP instrument makers and medical and scientific equipment specialists provide technical services to support research at NIH. SES staff produce sophisticated instruments containing electronic components, large or miniature mechanical components, polymers, and glass. SES also offers intramural researchers a variety of comprehensive plans for maintenance and repair of scientific equipment, clinical equipment, and personal computers. The Scientific Equipment Resources Program sells and leases often-sought scientific equipment, offering investigators shortened procurement times, flexibility in configuring their laboratories, and cost savings.

Research Highlights

A patient is undergoing surgical treatment for syringomyelia, a rare neurological disorder of unknown cause. BEIP scientists and engineers have developed instrumentation to measure, record, and evaluate fluid pressure changes in the spinal cord of syringomyelia patients.

Photo courtesy of the National Institute of Neurological Disorders and Stroke

Resources for Clinical Studies

Syringomyelia. A rare neurological disorder of unknown cause, syringomyelia primarily affects young adults, causing paralysis, loss of sensation, and pain. The disease is characterized by abnormal fluid-filled cavities in the spinal cord.

To date the most effective treatment for syringomyelia has not been established, but BEIP engineers are collaborating with scientists at the National Institute of Neurological Disorders and Stroke to study disease progression and perhaps pinpoint more effective treatment guidelines. This study draws on the talents of BEIP researchers in the Mechanical Engineering and Applied Clinical Engineering sections.

In clinical trials that began in FY 1992 the scientists are evaluating physiological and anatomical data from approximately 10 patients treated surgically for syringomyelia. Because evidence suggests that the disease is related to abnormal dynamics of cerebrospinal fluid, BEIP engineers have developed methods to measure and record fluid pressure at multiple sites along the spinal cord.

Other BEIP scientists are developing computer programs to analyze the data, looking for correlations among physiological data and structural details obtained by magnetic resonance imaging, ultrasonography, and computerized tomography. A better understanding of disease progression may help physicians identify optimal therapies for syringomyelia.

Modeling Delivery of Cancer-Fighting Drugs. To find the optimal method for delivering cancer-fighting drugs to tumors, scientists in the Chemical Engineering Section of BEIP are collaborating with researchers at the National Cancer Institute to model the flow of drugs through the arteries of major organs. The goal is to deliver high, uniform concentrations of toxic chemicals to tumor sites while minimizing harmful effects on the rest of the body.

In previous collaborative studies with the National Institute of Neurological Disorders and Stroke, BEIP engineers built a transparent model of the major vasculature that supplies the brain. A red dye was injected into the system to mimic intra-arterial drug delivery. The model showed that conventional methods for administering drugs via an artery often allowed the drug to remain in a separate stream—sometimes streaming away from the targeted artery and tumor—instead of uniformly mixing with the blood.

A specialized pump developed by BEIP engineers eliminated the streaming problem in the glass models and in later animal studies. A clinical trial on 10 patients who received intra-arterial chemotherapy for malignant brain tumors recently confirmed that the drug pump leads to more uniform drug delivery to the brain.

Turning their attention to the treatment of cervical cancer, the engineers have now built a glass model of the major pelvic arteries that supply the uterus and cervix. Research is in progress to determine the optimal infusion site, catheter design, and injection procedures that will deliver anticancer drugs to tumors while avoiding sensitive tissues around the uterus and the rectum. Clinical trials to test the selected methodology are expected to begin in approximately 1 year.

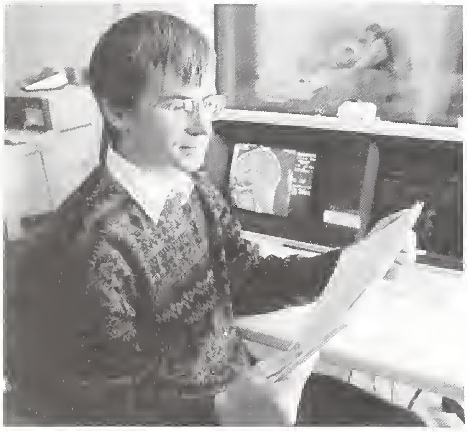
Special Instrumentation

Ultrasensitive Microcalorimeter. When scientists at the National Cancer Institute (NCI) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) decided to study interactions between DNA and tiny amounts of an immunosuppressive protein, they found that no commercially available instruments could provide the reliable measurements they needed. The investigators turned to the BEIP Applied Clinical Engineering Section, whose engineers had already designed and built an ultrasensitive stopped-flow microcalorimeter in collaboration with scientists at the National Heart, Lung, and Blood Institute. This instrument can measure protein-DNA bond interactions in very small samples.

In collaboration with BEIP, the NCI and NIDDK researchers used the microcalorimeter to study how the immunosuppressive protein called Cro binds to different stretches of DNA molecules. In the long run these studies are expected to shed light on how various proteins can be used to modify the immune system, which is of particular interest in the areas of organ transplantation, AIDS, and chemotherapy research. BEIP engineers are now developing a second-generation microcalorimeter to meet the needs of the investigators more specifically.

Analytical Electron Microscope Facility. Employing a technique called electron energy-loss spectroscopy (EELS), scientists in the electron beam imaging and microspectroscopy group of BEIP are able to locate very small numbers of atoms in tissues and biomolecular complexes. In perhaps the finest example of microanalysis to date, the researchers detected a mere four atoms of iron bound to a single hemoglobin molecule. The EELS technique is performed using a scanning transmission electron microscope.

BEIP scientists are now collaborating with investigators at the National Institute of Neurological Disorders and Stroke to detect minute quantities of calcium in thin slices of brain tissue. Calcium is of particular interest in cell biology because it serves as an intracellular messenger for many biological functions. In recent studies of the mouse brain the researchers measured calcium in the mitochondria and endoplasmic reticulum (ER) of neurons. Although these organelles contain very few calcium atoms, scientists postulate that the ER regulates calcium concentration during signal transmission. The finding that calcium concentration is more than three times higher in ER than in mitochondria seems to support a calcium-regulating role for ER. Future studies are expected to provide even more insights into the physiology of neurons.



Dr. Chrit Moonen analyzes results on an imager in the NIH In Vivo NMR Research Center. Dr. Moonen uses magnetic resonance imaging to study brain metabolism, follow metabolite transport in the body, and measure blood volume changes during cognitive, motor, or visual stimulation tests.

Ernie Branson, NCRR

Biomedical Imaging

Advances in Functional MRI at the In Vivo NMR Research Center. Using conventional magnetic resonance imaging (MRI), researchers can study a patient's internal anatomy noninvasively, without the use of harmful ionizing radiation. Functional MRI takes this technology a couple of steps further, combining structural details with chemical and physiological analyses. Functional MRI allows scientists to study not only the gross appearance of internal organs and tissues but also metabolic and biophysical processes in various regions of the body.

Engineers and physicists at the NIH In Vivo NMR Research Center are on the cutting edge in developing new technologies and applications for functional MRI. At this BEIP-managed center intramural scientists study patients, normal volunteers, and laboratory animals in research areas ranging from cancer treatment to blood flow to Alzheimer's disease.

In collaboration with scientists at the National Institute of Neurological Disorders and Stroke, BEIP engineers have improved on standard methods for imaging certain chemical compounds in the human brain, particularly metabolites that are associated with brain tumors. With further refinements these techniques may be used for earlier detection of brain tumors and malignant changes, since chemical changes occur before anatomical changes. These methods may also be used to evaluate the effectiveness of experimental cancer therapies.

In FY 1992 engineers at the In Vivo NMR Research Center also developed a new imaging technique known as echo-shifted MRI, which allows scientists to track changes in the blood volume of the brain. Because blood volume changes in response to many different pathologies, this technique holds potential as a noninvasive diagnostic tool. Collaborative studies in this area are now under way with researchers at the National Institute of Mental Health.

Imaging Small Animals. As a prelude to diagnostic studies of humans, nuclear imaging of small animals such as rabbits, monkeys, and guinea pigs can provide vital information about physiological events within the body. However, expensive imaging instrumentation such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) scanners are scarce and are often in demand for clinical studies rather than basic animal research.

To provide biomedical investigators with an alternative to costly clinical instruments for the study of small animals, researchers in the Applied Clinical Engineering Section of BEIP are designing a relatively inexpensive imaging system that can perform the full range of nuclear imaging procedures commonly conducted on human subjects. Using this scintigraphic imaging system, investigators will be able to screen new tracer techniques and radiopharmaceuticals in animals before administering them to patients.

In collaboration with scientists in the Nuclear Medicine Department of the NIH Clinical Center, BEIP engineers have designed and built a single-camera imaging system that produces high-resolution, two-dimensional images. By slowly rotating an animal on a platform, three-dimensional SPECT analyses also can be obtained. Future plans include improving the resolution of images, adding a second camera, and performing PET scans.

The final cost of the system is expected to be approximately $75,000, compared to about $350,000 for a SPECT system and several million dollars for a PET scanner. Ultimately, the researchers say, this inexpensive system may also be used clinically to study small organs or tissues like the thyroid gland.

Allen Markowitz (front) and Tom Tedder are developing a scintigraphic imaging system that will be able to produce high-resolution images of organ function in small animals. Once complete, this instrument will allow noninvasive studies of the effects of drugs and other interventions on physiological processes.

Ernie Branson, NCRR

Library Branch

Program Description

The NIH Library is the biomedical research library of the National Institutes of Health. It serves as the primary literature, referral, and information resource in the biomedical sciences for the administrative, scientific, and clinical staff of the NIH. A library annex located a few miles away serves as a reference resource to NIH staff in that area.

The 56-member staff provides a diverse range of services including photocopying, a clinical library service, translation into English of scientific papers published in foreign languages, compilation of bibliographies, and teaching bibliography-related courses.

The library maintains a comprehensive current journal collection in biomedical and related scientific research fields and a small collection in administrative literature. Infrequently requested materials are not maintained in the collection, but the library's extensive reciprocal borrowing agreements with other institutions allow it to obtain these materials for staff in a timely manner. Full-text databases are utilized by interlibrary loan staff to obtain copies of articles from newspapers and trade publications not easily obtained through other sources.

Books are reshelved continuously during working hours, with approximately 650,000 volumes reshelved in a year. Most volumes are reshelved within 1 to 2 hours of receipt.

Librarians who specialize in library software applications offer advice and assistance in using software to manage small collections or create bibliographies. The library also offers tutorials and classes in basic searching techniques using standard MEDLINE and Grateful Med, a program designed by the National Library of Medicine (NLM). The library has access to more than 400 computerized databases, including those on the systems DIALOG, GenInfo, MEDLARS, BRS, STN, and Mead Data Central. The library staff performs approximately 1,100 computer searches each month. Selective dissemination of information services is also available to NIH staff. Approximately 450 searches are stored on SDILINE, TOXLINE, AIDSLINE, and CANCERLINE, with monthly bibliographies distributed.

To improve NIH user access to the library materials, the NIH Library has continued to move forward in automation. A local area network, installed in 1991, now allows convenient access to the library's automated catalog. A new feature, installed in 1992, allows users to request library materials through the online catalog. This service complements the Loansome Doc addition to Grateful Med, which allows NIH users with a special code to order journal articles from this library while searching MEDLINE or other NLM databases.

In the reference area six microcomputers are provided for NIH staff to conduct their own literature searches via MEDLINE, a cumulative index to nursing and allied health literature, *Science Citation Index*, and *Psychological Abstracts*. The newest computer product located in this area is the *Online Journal of Current Clinical Trials,* an electronic journal published by the American Association for the Advancement of Science. This is the NIH Library's first subscription to an online journal.

The popular photocopy service grew 18 percent over FY 1991 to a total of 5.3 million copies. In FY 1992 the library staff filled 200,000 document requests, 30 percent more requests than in 1991. Approximately 98 percent of document requests are filled; 83 percent of them from within the NIH Library collection, the rest from nearby libraries.

The two-person translation unit fills approximately 450 requests per year in six languages. Urgent communications and patient records are handled immediately by staff; research papers of less urgency are translated and reproduced with desktop publishing.

In FY 1992 the Technical Services Section completed production of the 7th edition of *Current and Noncurrent Journals, NIH Library, 1991*. The staff edited the contents and designed the cover of this publication, which was distributed throughout NIH.

The NIH Library is open 365 days a year. Although the library is intended as a resource for the NIH community, the public is welcome to use its extensive resources for research purposes. Carrels are available for NIH patrons who require space and privacy for preparation of speeches, papers, or other work.

Library technician Omar Echegoyen processes reprint requests in the NIH Library. Through the interlibrary loan service approximately 900 requests are filled each day, and approximately 97 percent of the requests are completed and mailed within 3 working days.

Ernie Branson, NCRR

Use of the NIH Library continues to increase. Each month more than 30,000 people enter the library, and 3,000 to 4,000 books are circulated. Journals do not circulate unless there is more than one copy of a particular title. The integrated computer system controls acquisitions, catalog, series, and circulation functions. Journal holdings also appear in the catalog, with daily receipts visible on screen. The number of people entering the library, the number of photocopy requests, and the number of items reshelved all bear testimony to the fact that the NIH Library provides a vital and well-utilized resource.

Medical Arts and Photography Branch

Program Description

MAPB photographer John Crawford takes pictures of a surgeon at the National Cancer Institute as she inserts an indwelling catheter for chemotherapy in a cancer patient. MAPB produces most of the poster and publication designs, videotapes, photographs, exhibits, and graphics used at NIH.
Bill Branson, NCRR

The Medical Arts and Photography Branch (MAPB) produces a wide variety of visual documentation of scientific data, research programs, events, and accomplishments for NIH staff. Visual communications media produced by MAPB are used by NIH scientists in publications, exhibits, and presentations to the scientific community and the general public. Over 75,000 requests for services were completed in FY 1992.

MAPB's staff includes professional artists, photographers, and audiovisual specialists who produce communication materials ranging from slides, viewgraphs and other projected visual aids to exhibit designs, statistical drafting, display charts, posters, medical illustrations, publication design, videotapes, and support for special events.

This year MAPB produced five video films that received the Gold Screen Award from the National Association of Government Communicators. The chief of the design section received the NIH Director's Award. Several MAPB illustrators won honorable mention or Blue Pencil Awards in the fifth Annual Exhibition of the Illustrator's Club of Washington, Maryland, and Virginia.

MAPB services are comparable to, or exceed, commercially available services in professional quality and price. To assure both quality and price, competing qualified vendors participate in daily bid sessions. So that MAPB clients can benefit from the rapidly changing techniques of visual communications, new vendors are continually being interviewed.

MAPB is divided into four sections: Graphics, Photography, Medical Illustration, and Design. The Graphics Section includes the Special Events Unit and the Video Unit. The Graphics Section provides materials used for scientific presentations and publications, including illustrations, charts, graphs, tables, flow charts, slide presentations, and computer-generated graphics. The Special Events Unit provides support for one-time or unusual events or exhibits. One such event is the Medicine for the Public lecture series held each fall at NIH. The Special Events Unit also produces signs for the NIH campus and NIH buildings, and charts for congressional hearings. The Video Unit provides in-house videotaping, script writing, production of shows used for public service announcements, video news releases, new drug therapy videos, patient videos, training videos, and videotaping of NIH special events. Visual information specialists, an exhibit specialist, and TV production specialists work with clerical support within the section to provide these services.

MAPB's Photography Section provides central photographic services to the NIH community, including information and patient photography, clinical and surgical photography, micro- and macrophotography, and photographic laboratory processing. Staff members use a diverse range of photographic equipment to accommodate the large number of requests received each day.

The Medical Illustration Section produces a wide variety of continuous tone, line, and color medical illustrations of surgical gross pathological, biological, and dental subjects. In addition, the Medical Illustration Section provides illustrations for poster design, publications, exhibits, and newsletters. This section often participates in long-term illustration projects, such as an atlas or monograph, that require over 50 illustrations.

The Design Section of MAPB provides print design for publication information projects, scientific presentations, conferences, editorial and technical illustrations, and other services requested by clients. Its creative and talented artists produce graphic designs for printed materials that visually broadcast the NIH research mission.

To maintain and improve its high quality standards and meet changing requirements, MAPB's technology and skills are continuously being improved. The Graphics and Design Sections updated computer software to keep up with NIH researchers' increasing computer graphic needs. The Graphics Section purchased a Varitype 4000 Typesetter, which enables clients to bring their graphic images to MAPB on disk and have them printed out as camera-ready art. The Graphics Section is now able to provide high-quality graphic typesetting, imaging, and floppy conversion from IBM to Macintosh or vice versa as an in-house service. The Medical Illustration Section purchased computer technology to enhance biomedical drawings and reproductions. The Photography Section added a new microscope that provides video output, hard copy, and digital output.

Veterinary Resources Program

Program Description

The Veterinary Resources Program (VRP) facilitates intramural research by providing comprehensive, centralized professional and technical support for NIH biomedical research using animals.

The VRP completed an extensive reorganization in June 1991 to increase efficiency and centralize management control. A local area network (LAN) enhances communication between organizational units, and an administrative management services team supports the Office of the Director in providing centralized support services to the program's operational branches, sections, and units. The two branches of VRP each comprise three sections. The Research Animal Branch includes the Carnivore and Ungulate Section, the Primate Section, and the Rodent and Rabbit Section. The Scientific Services Branch consists of the Genetic Resource Section; the Laboratory Sciences Section; and the Surgery, Radiology, and Pharmacy Section.

The professional staff of VRP collaborates with intramural scientists to identify appropriate animal models, provide animal health surveillance and disease diagnosis, monitor nutritional needs, and assess caging requirements. A centralized pharmacy, which will serve the intramural community, is in the developmental stage. A variety of animals are housed in 7 centralized facilities on the NIH campus and in 12 facilities at the NIH Animal Center near Poolesville, Maryland.

The NIH Animal Genetic Resource is another component of the VRP. This collection of more than 300 rodent and rabbit strains and stocks is maintained to serve as models for the study of human diseases. Breeding nuclei from this resource are provided to public and private institutions worldwide. The resource has been designated by the World Health Organization as a Collaborating Centre for Defined Laboratory Animals and by the International Council for Laboratory Animal Science as a Nude Mouse Repository.

In FY 1992 the program focused on renovating existing central animal facilities in support of the NIH-wide effort to obtain accreditation from the American Association for Accreditation of Laboratory Animal Care. One of the projects includes a new small ungulate facility at the NIH Animal Center to be completed by October 1994. All facilities within the program are slated for extensive renovations and/or new construction throughout 1994 and 1995.

In keeping with the premise that good science and good animal care go hand-in-hand, the VRP added a veterinary behaviorist and associated staff to implement a new animal behavior program. This team employs a variety of techniques to enrich the living environment of laboratory animals—including nonhuman primates, dogs, cats, and pigs—housed at NIH facilities. This program is considered one of the foremost of its kind in the country and has now been enthusiastically implemented in other areas of NIH.

Gretchen Strange, a biologist in the Behavior and Nutrition Unit at the NIH Animal Center, participates in the environmental enrichment program for cats and other animals. By being handled and talked to, the animals become accustomed to a variety of stimuli and are less likely to develop behavioral abnormalities.

Veterinary Resources Program, NCRR

Research Highlights

Environmental Enrichment

Nonhuman Primates. In recent years animal researchers have been actively pursuing new ways to enrich the habitats of laboratory animals. Nonhuman primates pose a particularly challenging problem for behavioral scientists because, by law, primates must be housed in surroundings that promote their "psychological well-being."

In attempts to meet this Federal mandate, behavioral researchers in the VRP are evaluating techniques that encourage captive monkeys to engage in activities normally expressed in the wild. When animals spend more time performing species-typical behaviors such as foraging, grooming, and social interactions, they are less likely to engage in abnormal behaviors frequently seen in captive monkeys. These abnormal activities can include cage or self biting, repetitive pacing and rocking, and hair plucking.

Because free-ranging monkeys normally spend long periods of time foraging for food—in some cases foraging is their most time-consuming daytime activity—the scientists devised a "foraging board" that allows laboratory animals to search for their meals.

Dr. Michael Eckhaus (left) and Tom Spencer examine a rat for parasites in a new diagnostic pathology laboratory. The laboratory monitors the health of the NIH rodent research colonies by checking for viral, bacterial, and parasitic infections.

Ernie Branson, NCRR

The board, a sheet of plexiglass covered with a textured material such as fleece or artificial turf, attaches to the outside of the cage. Researchers rub particles of food into the board to encourage foraging behavior and to supplement the twice-daily feedings of biscuits. Subsequent studies showed that monkeys not only spend a considerable amount of time gathering food from the boards but also engage in less abnormal behavior. These foraging boards have since been patented and are now produced commercially.

Dogs and Cats. The habitats of dogs and cats housed in VRP facilities are also enriched. Personnel work with the animals to help them become accustomed to a variety of stimuli and environments, which provides greater ease of handling once the animals reach a laboratory setting.

Pigs. Farmers have long noted that pent-up pigs tend to bite each others' tails, an unfortunate behavior that can lead to infections. To provide an alternative to this natural tendency, VRP scientists have suspended chains within the pens. As pigs play with the chains, they are distracted from tail biting. The animals are also given balls to nuzzle, which encourages expression of the rooting behavior normally exhibited in the wild.

Rodents. In collaboration with VRP's genetic researchers, behavioral scientists are developing a research protocol to evaluate strategies for enriching the containment quarters of laboratory mice. The protocol is designed to identify environmental factors that can improve the breeding performance of certain strains. If the strategies prove beneficial, the scientists plan to implement these changes in the rodent breeding colonies.

Renovated Animal and Testing Facilities

Pathology and Diagnostic Laboratories Offer Expanded Services. Highly infectious agents such as mouse hepatitis virus and Sendai virus can quickly infiltrate a mouse colony, adversely affecting both the health of the animals and the quality of experimental data. Agents such as lymphocytic choriomeningitis virus can be transmitted from animals to humans, posing health hazards to laboratory workers. To help prevent the outbreak of animal diseases, the VRP provides routine diagnostic services for all species of laboratory animals used at NIH.

In FY 1992 VRP established a new Rodent Health Surveillance Program that is available to all NIH institutes, centers, and divisions. This program includes regular monitoring of "sentinel" animals to identify any infectious agents that may have been inadvertently introduced to animal colonies. During this fiscal year a variety of rodents were evaluated through this program, which is designed to identify subclinical infections that can significantly affect animal health, quality of research, or personnel safety. Each examination includes a complete autopsy, blood serum analyses for viral and bacterial pathogens, bacterial and mycoplasmal cultures, and examinations for internal or external parasites.

In FY 1992 VRP also completed extensive renovations of its necropsy laboratories where animal autopsies are performed. The renovation introduced state-of-the-art equipment and necropsy tables that facilitate safe and efficient animal examination.

Results of diagnostic procedures and health surveillance testing are maintained in a database that allows VRP staff to easily track the health status of animals maintained in NIH facilities.

Centralized Rabbit and Rodent Facility. A $6 million renovation has converted the building that once housed the NIH Clinical Center's surgical wing and blood bank to a state-of-the-art animal facility managed by the VRP. This 5-floor, centralized facility features 49 animal-holding rooms and 15 research procedure rooms.

Dr. Wayne O'Brien works with germ-free mice in a new NIH facility for rabbits and rodents.

Ernie Branson, NCRR

Today about 300 research protocols—conducted by scientists throughout NIH—are under way in the building. Investigations range from evaluating tumor treatment to studying diabetes to treating atherosclerosis and stroke. Among the facility's advanced equipment are a computerized monitoring system that helps maintain a stable physical environment in the animal rooms, computerized cage-washing machines, and a variety of radiological instruments.

National Center for Research Resources

The National Center for Research Resources (NCRR) supports NIH intramural and extramural biomedical research that includes clinical research studies, development and studies of animal and other models of human diseases or disorders, basic biomedical research, and instrumentation research. NCRR also supports the operation of technology resources and computer facilities as well as research centers in academic institutions with large minority enrollments. In addition, NCRR provides the NIH intramural scientific community with library services and medical arts and photography services. The activities and services of the NCRR—and publications that describe them—are listed on this page. For more detailed information about particular NCRR programs or the resources they support, contact the program directors at the numbers listed.

NCRR Extramural Research Resources comprise seven programs:

- **Biological Models and Materials Research Program**
  Telephone: (301) 594-7906
- **Biomedical Research Support Program**
  Telephone: (301) 594-7947
- **Biomedical Research Technology Program**
  Telephone: (301) 594-7934
- **Comparative Medicine Program**
  Telephone: (301) 594-7933
- **General Clinical Research Centers Program**
  Telephone: (301) 594-7945
- **Research Centers in Minority Institutions Program**
  Telephone: (301) 594-7944
- **Research Facilities Improvement Program**
  Telephone: (301) 594-7934

NCRR Intramural Research Resources comprise two programs and two branches:

- **Biomedical Engineering and Instrumentation Program**
  Telephone: (301) 496-4741
- **Veterinary Resources Program**
  Telephone: (301) 496-2527
- **Library Branch**
  Telephone: (301) 496-2447
- **Medical Arts and Photography Branch**
  Telephone: (301) 496-2868

NCRR Publications:

- The *Research Resources Reporter* is a newsletter that describes NCRR-supported biomedical findings and research in progress at universities, medical centers, and other research institutions across the United States. The *Reporter* also describes research services available to biomedical investigators and publishes a question-and-answer column relating to research resources.
- The NCRR *Access Guide* provides a comprehensive overview of the intramural and extramural components of NCRR and the research and service facilities supported by NCRR. The booklet also contains a directory of NCRR-supported grants that includes general grant descriptions as well as eligibility and evaluation criteria and application procedures.
- *Program Highlights* is an annual report of research accomplishments and significant services of each NCRR program and branch during the fiscal year. Detailed budget information about NCRR is also provided.
- *General Clinical Research Centers*, an NCRR directory, contains information about General Clinical Research Centers, their staffs, resources, and major areas of investigation. Investigators who receive their primary research funding from the National Institutes of Health are eligible to perform clinical research studies at the GCRC's.
- *Resources for Biomedical Research Technology*, an NCRR directory, lists resource centers supported by the Biomedical Research Technology Program, their staffs, resources, and major areas of investigation. The facilities are dedicated to applying the latest advances in the physical sciences, mathematics, computer science, and engineering to biomedical research. The facilities and their services are available to qualified investigators.
- *Resources for Comparative Biomedical Research*, an NCRR directory, contains information about specialized animal research and supply facilities, their staffs, types of resources, and major areas of research. The resources range from breeding facilities for lower animal forms to nonhuman primate research centers. These facilities and their services are available to qualified investigators.
- *Biological Models and Materials Research*, an NCRR directory, lists centers that study nonmammalian models for biomedical research—cells, lower organisms, computer simulations, and mathematical models—and resource centers that provide critical biomaterials. Nonmammalian organisms, viruses, bacteria, fungi, cell lines, human tissue, DNA probes, and chromosome libraries are available. The directory also lists the staffs, types of research, and major areas of investigation at each center. These facilities and services are available to qualified investigators.

All NCRR directories are updated and reissued periodically.

Single copies of NCRR publications may be obtained free of charge from the Research Resources Information Center, 1601 Research Boulevard, Rockville, MD 20850.
Telephone: (301) 251-4970.

Discrimination Prohibited: Under provisions of applicable public law enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contract may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, all programs of the National Center for Research Resources must be operated in compliance with these laws and Executive Orders.

Queries about the NCRR may be directed to
the Office of Science and Health Reports,
National Center for Research Resources,
Westwood Building, Room 10A15,
5333 Westbard Avenue, Bethesda, MD 20892.
Telephone: (301) 594-7938.

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